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14 Attorneys for Plaintiffs

15 TAKEDA PHARMACEUTICAL CO., LTD.,

16 TAKEDA PHARMACEUTICALS NORTH

17 AMERICA, INC., TAKEDA

18 PHARMACEUTICALS LLC, AND TAKEDA

19 PHARMACEUTICALS AMERICA, INC.

20 UNITED STATES DISTRICT COURT  
21 NORTHERN DISTRICT OF CALIFORNIA

22 TAKEDA PHARMACEUTICAL CO., LTD.,

23 TAKEDA PHARMACEUTICALS NORTH

24 AMERICA, INC., TAKEDA

25 PHARMACEUTICALS LLC, AND TAKEDA

26 PHARMACEUTICALS AMERICA, INC.,

27 Plaintiffs,

28 v.

29 HANDA PHARMACEUTICALS, LLC,

30 Defendant.

CASE NO.

COMPLAINT FOR PATENT  
INFRINGEMENT

E-filing

ORIGINAL  
FILED

FEB 23 2011

RICHARD W. WIEKING  
CLERK, U.S. DISTRICT COURT,  
NORTHERN DISTRICT OF CALIFORNIA

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1 Plaintiffs Takeda Pharmaceutical Company Limited, Takeda Pharmaceuticals North  
2 America, Inc., Takeda Pharmaceuticals LLC, and Takeda Pharmaceuticals America, Inc.  
3 (collectively, "Plaintiffs"), state the following as their Complaint against Defendant Handa  
4 Pharmaceuticals, LLC:

5 **I.**

6 **THE PARTIES**

7 1. Plaintiff Takeda Pharmaceutical Company Limited ("TPC") is a Japanese corporation  
8 with its principal place of business at 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan. As part of  
9 its business, TPC is involved in the research, development, and marketing of pharmaceutical  
10 products.

11 2. TPC is the owner of record and assignee of U.S. Patent No. 6,462,058 (the "'058  
12 Patent"), U.S. Patent No. 6,664,276 (the "'276 Patent"), U.S. Patent No. 6,939,971 (the "'971  
13 Patent"), U.S. Patent No. 7,285,668 (the "'668 Patent"), and U.S. Patent No. 7,790,755 (the "'755  
14 Patent") (collectively the "Asserted Patents").

15 3. Plaintiff Takeda Pharmaceuticals North America, Inc. ("TPNA"), is a Delaware  
16 corporation with its principal place of business at One Takeda Parkway, Deerfield, IL 60015. As  
17 part of its business, TPNA is involved in the research, development, and marketing of  
18 pharmaceutical products. TPNA is the registered holder of approved New Drug Application No. 22-  
19 287. In addition, TPNA has the exclusive right to import dextansoprazole delayed release capsules  
20 into the United States and sell those capsules to Takeda Pharmaceuticals LLC.

21 4. Plaintiff Takeda Pharmaceuticals LLC ("Takeda LLC") is a Delaware limited liability  
22 company, having a principal place of business at One Takeda Parkway, Deerfield, IL 60015. As part  
23 of its business, Takeda LLC is involved in the purchase and sale of pharmaceutical products.  
24 Takeda LLC is an exclusive licensee of the Asserted Patents.

25 5. Plaintiff Takeda Pharmaceuticals America, Inc. ("TPA"), is a Delaware corporation,  
26 having a principal place of business at One Takeda Parkway, Deerfield, IL 60015. As part of its  
27 business, TPA is involved in the purchase, sale, and marketing of pharmaceutical products. TPA has  
28

1 the exclusive right to purchase dextansoprazole delayed release capsules from Takeda LLC and sell  
2 those capsules to the public in the United States.

3 6. Plaintiffs are informed and believe, and thereupon allege, that defendant Handa  
4 Pharmaceuticals, LLC ("Handa"), is a limited liability company organized under the laws of  
5 California with its principal place of business at 39465 Paseo Padre Parkway, Suite 2600, Fremont,  
6 CA 94538.

7 7. Unless specifically stated otherwise, the acts complained of herein were committed  
8 by, on behalf of, and/or for the benefit of Handa.

9 **II.**

10 **NATURE OF THE ACTION**

11 8. This is an action for patent infringement.

12 9. Plaintiffs are informed and believe, and thereupon allege, that Handa has been and/or  
13 is infringing one or more claims of each of the Asserted Patents.

14 **III.**

15 **JURISDICTION AND VENUE**

16 10. This action arises under the patent laws of the United States, 35 U.S.C. § 1 *et seq.*,  
17 including 35 U.S.C. § 271. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331  
18 and 1338(a).

19 11. This Court has personal jurisdiction over Handa because Handa is a company  
20 organized under the laws of California, has its principal place of business within this district,  
21 conducts business in this district, purposefully avails itself of the rights and benefits of California  
22 law, and has been infringing, contributing to the infringement of and/or actively inducing others to  
23 infringe claims of the Asserted Patents in California and elsewhere.

24 12. Plaintiffs are informed and believe, and thereupon allege, that a substantial part of the  
25 events giving rise to Plaintiffs' claims occurred in the Northern District of California. Venue is  
26 proper in this Court pursuant to 28 U.S.C. §§ 1391(b), 1391(c), 1391(d) and/or 1400(b).

## IV.

**FACTUAL BACKGROUND****A. Asserted Patents****1. The '058 Patent**

13. On October 8, 2002, U.S. Patent No. 6,462,058, titled "Benzimidazole Compound Crystal," was duly and legally issued to Takeda Chemical Industries, Ltd., as assignee of named inventors Akira Fujishima, Isao Aoki, and Keiji Kamiyama. On June 29, 2004, Takeda Chemical Industries, Ltd., changed its name to Takeda Pharmaceutical Company Limited (i.e., TPC). The change of the name of the assignee of the '058 Patent to TPC was recorded in the United States Patent and Trademark Office ("PTO") on January 19, 2005. A true and correct copy of the '058 Patent is attached as Exhibit A to this Complaint.

14. The expiration date of the '058 Patent listed in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (published by the U.S. Food and Drug Administration ("FDA") and commonly known as the Orange Book) is June 15, 2020.

**2. The '276 Patent**

15. On December 16, 2003, U.S. Patent No. 6,664,276, titled "Benzimidazole Compound Crystal," was duly and legally issued to Takeda Chemical Industries, Ltd., as assignee of named inventors Akira Fujishima, Isao Aoki, and Keiji Kamiyama. On June 29, 2004, Takeda Chemical Industries, Ltd., changed its name to Takeda Pharmaceutical Company Limited (i.e., TPC). The change of the name of the assignee of the '276 Patent to TPC was recorded in the PTO on January 19, 2005. A true and correct copy of the '276 Patent is attached as Exhibit B to this Complaint.

16. The expiration date of the '276 Patent listed in the Orange Book is June 15, 2020.

**3. The '971 Patent**

17. On September 6, 2005, U.S. Patent No. 6,939,971, titled "Benzimidazole Compound Crystal," was duly and legally issued to Takeda Pharmaceutical Company Limited, as assignee of named inventors Akira Fujishima, Isao Aoki, and Keiji Kamiyama. A true and correct copy of the '971 Patent is attached as Exhibit C to this Complaint.

18. The expiration date of the '971 Patent listed in the Orange Book is June 15, 2020.

**4. The '668 Patent**

19. On October 23, 2007, U.S. Patent No. 7,285,668, titled "Process for the Crystallization of (R)- or (S)-Lansoprazole," was duly and legally issued to Takeda Pharmaceutical Company Limited, as assignee of named inventors Hideo Hashimoto and Tadashi Urai. A true and correct copy of the '668 Patent is attached as Exhibit D to this Complaint.

20. The expiration date of the '668 Patent listed in the Orange Book is June 15, 2020.

**5. The '755 Patent**

21. On September 7, 2010, U.S. Patent No. 7,790,755, titled "Controlled Release Preparation," was duly and legally issued to Takeda Pharmaceutical Company Limited, as assignee of named inventors Yohko Akiyama, Takashi Kurasawa, Hiroto Bando, and Naoki Nagahara. A true and correct copy of the '755 Patent is attached as Exhibit E to this Complaint.

22. The expiration date of the '755 Patent listed in the Orange Book is August 2, 2026.

**B. DEXILANT**

23. Plaintiff TPNA is the registered holder of approved New Drug Application No. 22-287 for the manufacture and sale of the drug dextlansoprazole, a proton pump inhibitor, for the treatment of all grades of erosive esophagitis, maintaining healing of esophagitis, and treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease ("GERD"). Plaintiff TPA sells dextlansoprazole in the United States under the trade name DEXILANT, in 30 mg and 60 mg dosage forms. The 30 mg and 60 mg dosage forms of DEXILANT were approved by the FDA on January 30, 2009.<sup>1</sup>

24. Upon information and belief, DEXILANT is the first and only acid reflux disease treatment specifically designed for the release of medicine in two stages over time. The key to the

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<sup>1</sup> Plaintiffs originally marketed the drug dextlansoprazole under the proprietary name KAPIDEX. On March 4, 2010, the FDA announced that TPNA would start marketing KAPIDEX under the new name DEXILANT to avoid potential confusion with two other medications, CASODEX and KADIAN.

1 second release is DEXILANT's Dual Delayed Release™ formulation ("DDR"). DDR combines two  
2 different types of granules in one pill. DEXILANT releases one dose of medicine within an hour of  
3 taking a pill. Then, around four to five hours later, DEXILANT releases a second dose of medicine.

4 25. The Asserted Patents are listed in the Orange Book in support of Plaintiffs'  
5 DEXILANT (dexlansoprazole) delayed release capsules, in 30 mg and 60 mg dosage forms.

6 **C. The ANDA and Subsequent Amendments**

7 26. On information and belief, Handa has submitted Abbreviated New Drug Application  
8 No. 202-294 (the "ANDA") to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act  
9 (21 U.S.C. § 355(j)). The ANDA seeks approval to market dexlansoprazole delayed release capsules  
10 in 30 mg and 60 mg dosage forms (the "Proposed Capsules") as a generic version of DEXILANT,  
11 prior to the expiration dates of the Asserted Patents.

12 27. Plaintiffs are informed and believe, and thereupon allege, that Handa filed the original  
13 ANDA on August 24, 2010. The ANDA as originally filed related only to the 60 mg dosage form  
14 and included a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (a "Paragraph IV Certification"),  
15 that the '058 Patent, the '276 Patent, the '971 Patent, and the '668 Patent are invalid or will not be  
16 infringed by the manufacture, use, or sale of the Proposed Capsules.

17 28. Plaintiffs are informed and believe, and thereupon allege, that Handa amended the  
18 ANDA on December 10, 2010, to add a Paragraph IV Certification with respect to the '755 Patent.

19 29. Plaintiffs are informed and believe, and thereupon allege, that Handa amended the  
20 ANDA on January 10, 2011, to add the 30 mg dosage form, and included a Paragraph IV  
21 Certification with respect to all of the Asserted Patents dated January 7, 2011.

22 30. Plaintiffs thus are informed and believe, and thereupon allege, that the ANDA as  
23 presently amended relates to both 30 mg and 60 mg dosage forms and contains Paragraph IV  
24 Certifications with respect to all of the Asserted Patents.

25 31. On January 14, 2011, TPNA received a letter (the "Notice Letter") from Handa by  
26 Federal Express delivery dated January 13, 2011, notifying TPNA and TPC that the ANDA includes  
27 a Paragraph IV Certification that, in Handa's opinion, the Asserted Patents are invalid,  
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unenforceable, or will not be infringed by the commercial manufacture, use, or sale of the Proposed Capsules. This was the first Notice Letter that any of the Plaintiffs received related to ANDA No. 202-294.<sup>2</sup>

32. The ANDA and its subsequent amendments do not provide any valid basis for concluding that the Asserted Patents are invalid, unenforceable, or will not be infringed by the commercial manufacture, use, or sale of the Proposed Capsules.

33. Plaintiffs are informed and believe, and thereupon allege, that the submission of the ANDA and its subsequent amendments to the FDA, including the Paragraph IV Certifications, constitutes infringement of the Asserted Patents under 35 U.S.C. § 271(e)(2). Moreover, any commercial manufacture, use, offer to sell, sale, or import of the Proposed Capsules would infringe the Asserted Patents under 35 U.S.C. § 271(a)–(c).

34. Plaintiffs commenced this action within 45 days of receiving the Notice Letter, as required by 21 U.S.C. § 355(j)(5)(B)(iii).

## V.

### **CLAIMS FOR RELIEF**

#### **COUNT I**

#### **(Patent Infringement of U.S. Patent No. 6,462,058 Under 35 U.S.C. § 271, *et seq.*)**

35. Plaintiffs incorporate by reference and reallege paragraphs 1 through 34 above as though fully restated herein.

36. The submission of the ANDA and its subsequent amendments to the FDA, including the Paragraph IV Certifications, constitutes infringement of the '058 Patent under 35 U.S.C. § 271(e)(2). Moreover, any commercial manufacture, use, offer to sell, sale, or import of the Proposed Capsules would infringe the '058 Patent under 35 U.S.C. § 271(a)–(c).

37. Handa's infringing activities will irreparably harm Plaintiffs unless enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

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<sup>2</sup> On January 18, 2011, TPNA received a second, similar letter from Handa sent by certified mail and dated January 12, 2011.

**COUNT II**

**(Patent Infringement of U.S. Patent No. 6,664,276  
Under 35 U.S.C. § 271, *et. seq.*)**

38. Plaintiffs incorporate by reference and reallege paragraphs 1 through 37 above as though fully restated herein.

39. The submission of the ANDA and its subsequent amendments to the FDA, including the Paragraph IV Certifications, constitutes infringement of the '276 Patent under 35 U.S.C. § 271(e)(2). Moreover, any commercial manufacture, use, offer to sell, sale, or import of the Proposed Capsules would infringe the '276 Patent under 35 U.S.C. § 271(a)–(c).

40. Handa's infringing activities will irreparably harm Plaintiffs unless enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

**COUNT III**

**(Patent Infringement of U.S. Patent No. 6,939,971  
Under 35 U.S.C. § 271, *et. seq.*)**

41. Plaintiffs incorporate by reference and reallege paragraphs 1 through 40 above as though fully restated herein.

42. The submission of the ANDA and its subsequent amendments to the FDA, including the Paragraph IV Certifications, constitutes infringement of the '971 Patent under 35 U.S.C. § 271(e)(2). Moreover, any commercial manufacture, use, offer to sell, sale, or import of the Proposed Capsules would infringe the '971 Patent under 35 U.S.C. § 271(a)–(c).

43. Handa's infringing activities will irreparably harm Plaintiffs unless enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

**COUNT IV**

**(Patent Infringement of U.S. Patent No. 7,285,668  
Under 35 U.S.C. § 271, *et. seq.*)**

44. Plaintiffs incorporate by reference and reallege paragraphs 1 through 43 above as though fully restated herein.

45. The submission of the ANDA and its subsequent amendments to the FDA, including the Paragraph IV Certifications, constitutes infringement of the '668 Patent under 35 U.S.C.



§ 271(e)(2). Moreover, any commercial manufacture, use, offer to sell, sale, or import of the Proposed Capsules would infringe the '668 Patent under 35 U.S.C. § 271(a)–(c).

46. Handa's infringing activities will irreparably harm Plaintiffs unless enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

### **COUNT V**

#### **(Patent Infringement of U.S. Patent No. 7,790,755 Under 35 U.S.C. § 271, et. seq.)**

47. Plaintiffs incorporate by reference and reallege paragraphs 1 through 46 above as though fully restated herein.

48. The submission of the ANDA and its subsequent amendments to the FDA, including the Paragraph IV Certifications, constitutes infringement of the '755 Patent under 35 U.S.C. § 271(e)(2). Moreover, any commercial manufacture, use, offer to sell, sale, or import of the Proposed Capsules would infringe the '755 Patent under 35 U.S.C. § 271(a)–(c).

49. Handa's infringing activities will irreparably harm Plaintiffs unless enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

### **VI.**

#### **PRAYER FOR RELIEF**

WHEREFORE, Plaintiffs pray for judgment as follows:

A. For a determination that Handa has infringed each of the Asserted Patents;

B. For a determination that the commercial use, sale, offer for sale, manufacture, and/or importation by Handa of the Proposed Capsules would infringe each of the Asserted Patents;

C. For a determination, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date for approval of the ANDA, under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), be no earlier than the expiration date of the last of the Asserted Patents, including any extensions or adjustments;

D. For an order preliminarily and permanently enjoining Handa and its affiliates, subsidiaries, officers, directors, employees, agents, representatives, licensees, successors, assigns,

1 and all those acting for them and on their behalf, or acting in concert with them directly or indirectly,  
2 from infringing the Asserted Patents; and

3 E. For such other and further relief as this Court deems just and proper.

4  
5  
6 DATED: February 23, 2010

Respectfully Submitted,

MUNGER, TOLLES & OLSON LLP

7  
8 By: 

JEFFREY I. WEINBERGER

9  
10 Attorneys for Plaintiffs  
11 TAKEDA PHARMACEUTICAL CO., LTD.,  
12 TAKEDA PHARMACEUTICALS NORTH  
13 AMERICA, INC., TAKEDA  
14 PHARMACEUTICALS LLC, AND TAKEDA  
15 PHARMACEUTICALS AMERICA, INC.  
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# **EXHIBIT A**



US006462058B1

(12) **United States Patent**  
**Fujishima et al.**

(10) **Patent No.:** **US 6,462,058 B1**  
(45) **Date of Patent:** **Oct. 8, 2002**

(54) **BENZIMIDAZOLE COMPOUND CRYSTAL**

(75) Inventors: **Akira Fujishima**, Sanda; **Isao Aoki**,  
Kawanishi; **Keiji Kamiyama**, Ibaraki,  
all of (JP)

(73) Assignee: **Takeda Chemical Industries, Ltd.**,  
Osaka (JP)

(\*) Notice: Subject to any disclaimer, the term of this  
patent is extended or adjusted under 35  
U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/674,624**

(22) PCT Filed: **Jun. 15, 2000**

(86) PCT No.: **PCT/JP00/03881**

§ 371 (c)(1),  
(2), (4) Date: **Nov. 3, 2000**

(30) **Foreign Application Priority Data**

Jun. 17, 1999 (JP) ..... 11-171509

(51) **Int. Cl.**<sup>7</sup> ..... **C07D 401/12**; A61K 31/4439

(52) **U.S. Cl.** ..... **514/338**; 546/273.7

(58) **Field of Search** ..... 546/273.7; 514/338

(56) **References Cited**

**FOREIGN PATENT DOCUMENTS**

EP 0174726 A1 3/1986

EP 0302720 A1 2/1989  
WO 92/08716 5/1992  
WO 96/02535 2/1996  
WO 96/17077 6/1996  
WO 97/02261 1/1997  
WO 98/21201 5/1998

**OTHER PUBLICATIONS**

CA 127:336721, Curin et al. 1997.\*

CA 127:362535, Vrecer et al. 1997.\*

CA 124:331460, Katsuki et al. 1996.\*

H. Katsuki et al. "Determination of R(+)- and S(-)-lanso-  
prazole using chiral stationary-phase liquid chromatography  
and their enantioselective pharmacokinetics in humans",  
Chemical Abstracts, vol. 124, No. 25, p. 19 (1996)  
(Abstract).

\* cited by examiner

*Primary Examiner*—Jane Fan

(74) *Attorney, Agent, or Firm*—Mark Chao; Elaine M.  
Ramesh

(57) **ABSTRACT**

A novel crystal of (R)-2-[[[3-methyl-4-(2, 2,2-  
trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-  
benzimidazole or a salt thereof of the present invention is  
useful for an excellent antiulcer agent.

**8 Claims, No Drawings**

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**BENZIMIDAZOLE COMPOUND CRYSTAL**

This application is the National Stage of International Application No. PCT/JP00/03881, filed on Jun. 15, 2000.

**TECHNICAL FIELD**

The present invention relates to a crystal of a benzimidazole compound showing antiulcer action.

**BACKGROUND ART**

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof having an antiulcer action is reported in JP-A-61-50978, etc.

There is a demand for a more stable and excellently absorbable antiulcer agent.

**DISCLOSURE OF INVENTION**

Having chiral sulfurin themolecular structure thereof, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole occurs in two kinds of optical isomers. After extensive exploration, the present inventors succeeded in optically resolving and crystallizing the (R)-isomer of 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, for the first time found that this crystal serves satisfactorily as a pharmaceutical, made further investigation based on this finding, and developed the present invention.

Accordingly, the present invention relates to:

- [1] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof;
- [2] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole;
- [3] a crystal according to the above [2] wherein the X-ray powder diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom;
- [4] a pharmaceutical composition which comprises the crystal according to the above [1];
- [5] a pharmaceutical composition according to the above [4], which is for treating or preventing digestive ulcer;
- [6] a method for treating or preventing digestive ulcer in a mammal in need thereof which comprises administering to said mammal an effective amount of the crystal according to the above [1] with a pharmaceutically acceptable excipient, carrier or diluent;
- [7] use of the crystal according to the above [1] for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer, and so forth.

The "salt" of "(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof" includes, for example, metal salts, salts with organic bases, salts with basic amino acids, and so forth. Preferred are physiologically acceptable salts.

Metal salts include, for example, alkali metal salts such as sodium salt and potassium salt; and alkaline earth metal salts such as calcium salt, magnesium salt and barium salt. Salts with organic bases include, for example, salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, etc. Salts with basic amino acids include, for example, salts with arginine, lysine, etc.

The crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof may be a hydrate or not.

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Said "hydrate" includes 0.5 hydrate to 5.0 hydrate. Among others, 0.5 hydrate, 1.0 hydrate, 1.5 hydrate, 2.0 hydrate and 2.5 hydrate are preferred. More preferred is 1.5 hydrate.

The crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluorobethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof can be produced by subjecting 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof to an optical resolution or subjecting 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole to an asymmetrical oxidization to obtain the (R)-isomer, followed by crystallizing the resultant isomer.

Methods of optical resolution include per se known methods, for example, a fractional recrystallization method, a chiral column method, a diastereomer method, and so forth. Asymmetric oxidation includes per se known methods.

The "fractional recrystallization method" includes a method in which a salt is formed between a racemate and an optically active compound [e.g., (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine, etc.], which salt is separated by fractional recrystallization etc., and, if desired, subjected to a neutralization process, to give a free optical isomer.

The "chiral column method" includes a method in which a racemate or a salt thereof is applied to a column for optical isomer separation (chiral column). In the case of liquid chromatography, for example, optical isomers are separated by adding a racemate to a chiral column such as ENANTIO-OVM (produced by Tosoh Corporation) or the DAICEL CHIRAL series (produced by Daicel Corporation), and developing the racemate in water, a buffer (e.g., phosphate buffer), an organic solvent (e.g., hexane, ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, triethylamine, etc.), or a solvent mixture thereof. In the case of gas chromatography, for example, a chiral column such as CP-Chirasil-DeX CB (produced by GL Science) is used to separate optical isomers.

The "diastereomer method" includes a method in which a racemate and an optically active reagent are reacted (preferably, an optically active reagent is reacted to the 1-position of the benzimidazole group) to give a diastereomer mixture, which is then subjected to ordinary separation means (e.g., fractional recrystallization, chromatography, etc.) to obtain either diastereomer, which is subjected to a chemical reaction (e.g., acid hydrolysis, base hydrolysis, hydrogenolysis, etc.) to cut off the optically active reagent moiety, whereby the desired optical isomer is obtained. Said "optically active reagent" includes, for example, an optically active organic acids such as MTPA [a-methoxy-a-(trifluoromethyl)phenylacetic acid] and (-)-menthoxyacetic acid; and optically active alkoxymethyl halides such as (1R-endo)-2-(chloromethoxy)-1,3,3-trimethylbicyclo[2.2.1]heptane, etc.

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof is produced by the methods described in JP-A-61-50978, U.S. Pat. No. 4,628,098 etc. or analogous methods thereto.

Methods of crystallization includes per se known methods, for example, a crystallization from solution, a crystallization from vapor, and a crystallization from molten form.

Methods of the "crystallization from solution" include, for example, a concentration method, a slow cooling method, a reaction method (diffusion method, electrolysis method), a hydrothermal growth method, a fusing agent method, and so forth. Solvents to be used include, for example, aromatic hydrocarbons (e.g., benzene, toluene, xylene, etc.), pharmaceutical composition with good repro-

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ducibility. In addition, when orally administered, the crystal of the present invention is more absorbable and more rapidly shows its action than the racemate. In addition, when administered, the crystal of the present invention shows a higher C<sub>max</sub> (maximum blood concentration) and a greater AUC (area under the concentration-time curve) than the racemate, and becomes less likely to be metabolized partly because of the increased protein-binding rate, thus showing an extended duration of action. The crystal of the present invention is therefore useful as a pharmaceutical of low doses and with a low prevalence of adverse reactions.

The crystal of the present invention is useful in mammals (e.g., humans, monkeys, sheep, bovines, horses, dogs, cats, rabbits, rats, mice, etc.) for the treatment and prevention of digestive ulcer (e.g., gastric ulcer, duodenal ulcer, stomal ulcer, Zollinger-Ellison syndrome, etc.), gastritis, reflux esophagitis, NUD (non-ulcer dyspepsia), gastric cancer and gastric MALT lymphoma; *Helicobacter pylori* eradication; suppression of upper gastrointestinal hemorrhage due to digestive ulcer, acute stress ulcer and hemorrhagic gastritis; suppression of upper gastrointestinal hemorrhage due to invasive stress (stress from major surgery necessitating intensive management after surgery, and from cerebral vascular disorder, head trauma, multiple organ failure and extensive burns necessitating intensive treatment); treatment and prevention of ulcer caused by a nonsteroidal anti-inflammatory agent; treatment and prevention of hyperacidity and ulcer due to postoperative stress; pre-anesthetic administration etc.

The crystal of the present invention is of low toxicity, and can be safely administered orally or non-orally (e.g., topical, rectal and intravenous administration, etc.), as such or in the form of pharmaceutical compositions formulated with a pharmacologically acceptable carrier, e.g., tablets halogenated hydrocarbons (e.g., dichloromethane, chloroform, etc.), saturated hydrocarbons (e.g., hexane, heptane, cyclohexane, etc.), ethers (e.g., diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, etc.), nitriles (e.g., acetonitrile, etc.), ketones (e.g., acetone, etc.), sulfoxides (e.g., dimethylsulfoxide, etc.), acid amides (e.g., N,N-dimethylformamide, etc.), esters (e.g., ethyl acetate, etc.), alcohols (e.g., methanol, ethanol, isopropyl alcohol, etc.), water, and so forth. These solvents may be used singly or in mixtures of two or more kinds in appropriate ratios (e.g., 1:1 to 1:100).

Methods of the "crystallization from vapor" include, for example, a gasification method (sealed tube method, gas stream method), a gas phase reaction method, a chemical transportation method, and so forth.

Methods of the "crystallization from molten form" include, for example, a normal freezing method (pulling-up method, temperature gradient method, Bridgman method), a zone melting method (zone leveling method, float zone method), a special growth method (VLS method, liquid phase epitaxis method), and so forth.

For analyzing the crystal obtained, X-ray diffraction crystallographic analysis is commonly used. In addition, crystal orientation can also be determined by a mechanical method, an optical method, etc.

A thus obtained crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof (hereinafter also referred to as "crystal of the present invention") is useful as a pharmaceutical because it shows excellent antiulcer action, gastric acid secretion-inhibiting action, mucosa-protecting action, anti-*Helicobacter pylori* action, etc., and because it is of low toxicity. Furthermore, by crystallizing the (R)-isomer, not only its stability is improved but also its handling is facilitated so that it can be prepared as a solid (including sugar-coated tablets and film-coated tablets), powders, granules, capsules (including soft capsules), orally disinte-

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grating tablets, liquids, injectable preparations, suppositories, sustained-release preparations and patches, in accordance with a commonly known method.

The content of the crystal of the present invention in the pharmaceutical composition of the present invention is about 0.01 to 100% by weight relative to the entire composition. Varying depending on subject of administration, route of administration, target disease etc., its dose is normally about 0.5 to 1,500 mg/day, preferably about 5 to 150 mg/day, based on the active ingredient, for example, when it is orally administered as an antiulcer agent to an adult human (60 kg). The crystal of the present invention may be administered once daily or in 2 to 3 divided portions per day.

Pharmacologically acceptable carriers that may be used to produce the pharmaceutical composition of the present invention include various organic or inorganic carrier substances in common use as pharmaceutical materials, including excipients, lubricants, binders, disintegrants; water-soluble polymers and basic inorganic salts for solid preparations; and solvents, dissolution aids, suspending agents, isotonicizing agents, buffers and soothing agents for liquid preparations. Other ordinary pharmaceutical additives such as preservatives, antioxidants, coloring agents, sweetening agents, souring agents, bubbling agents and flavorings may also be used as necessary.

Such "excipients" include, for example, lactose, sucrose, D-mannitol, starch, cornstarch, crystalline cellulose, light silicic anhydride and titanium oxide.

Such "lubricants" include, for example, magnesium stearate, sucrose fatty acid esters, polyethylene glycol, talc and stearic acid.

Such "binders" include, for example, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, crystalline cellulose,  $\alpha$ -starch, polyvinylpyrrolidone, gum arabic powder, gelatin, pullulan, and low-substitutional hydroxypropyl cellulose.

Such "disintegrants" include (1) crosslinked povidone, (2) what is called super-disintegrants such as crosslinked carmellose sodium (FMC-Asahi Chemical) and carmellose calcium (Gotoku Yakuhin), (3) carboxymethyl starch sodium (e.g., product of Matsutani Chemical), (4) low-substituted hydroxypropyl cellulose (e.g., product of Shin-Etsu Chemical), (5) cornstarch, and so forth. Said "crosslinked povidone" may be any crosslinked polymer having the chemical name 1-ethenyl-2-pyrrolidinone homopolymer, including polyvinylpyrrolidone (PVPP) and 1-vinyl-2-pyrrolidinone homopolymer, and is exemplified by Colidon CL (produced by BASF), Polyplasdon XL (produced by ISP), Polyplasdon XL-10 (produced by ISP) and Polyplasdon INF-10 (produced by ISP).

Such "water-soluble polymers" include, for example, ethanol-soluble water-soluble polymers [e.g., cellulose derivatives such as hydroxypropyl cellulose (hereinafter also referred to as HPC), polyvinylpyrrolidone] and ethanol-insoluble water-soluble polymers [e.g., cellulose derivatives such as hydroxypropylmethyl cellulose (hereinafter also referred to as HPMC), methyl cellulose and carboxymethyl cellulose sodium, sodium polyacrylate, polyvinyl alcohol, sodium alginate, guar gum].

Such "basic inorganic salts" include, for example, basic inorganic salts of sodium, potassium, magnesium and/or calcium. Preferred are basic inorganic salts of magnesium and/or calcium. More preferred are basic inorganic salts of magnesium. Such basic inorganic salts of sodium include, for example, sodium carbonate, sodium hydrogen carbonate, disodium hydrogenphosphate, etc. Such basic inorganic salts of potassium include, for example, potassium carbonate, potassium hydrogen carbonate, etc. Such basic inorganic salts of magnesium include, for example, heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate



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aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite  $[Mg_6Al_2(OH)_{16}CO_3 \cdot 4H_2O]$ , alumina hydroxide magnesium, and so forth. Among others, preferred is heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, etc. Such basic inorganic salts of calcium include, for example, precipitated calcium carbonate, calcium hydroxide, etc.

Such "solvents" include, for example, water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil and olive oil.

Such "dissolution aids" include, for example, polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate and sodium citrate.

Such "suspending agents" include, for example, surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and monostearic glycerol; and hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose.

Such "isotonizing agents" include, for example, glucose, D-sorbitol, sodium chloride, glycerol and D-mannitol.

Such "buffers" include, for example, buffer solutions of phosphates, acetates, carbonates, citrates etc.

Such "soothing agents" include, for example, benzyl alcohol.

Such "preservatives" include, for example, p-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid.

Such "antioxidants" include, for example, sulfites, ascorbic acid and  $\alpha$ -tocopherol.

Such "coloring agents" include, for example, food colors such as Food Color Yellow No. 5, Food Color Red No. 2 and Food Color Blue No. 2; and food lake colors and red oxide.

Such "sweetening agents" include, for example, saccharin sodium, dipotassium glycyrrhetinate, aspartame, stevia and thaumatin.

Such "souring agents" include, for example, citric acid (citric anhydride), tartaric acid and malic acid.

Such "bubbling agents" include, for example, sodium bicarbonate.

Such "flavorings" may be synthetic substances or naturally occurring substances, and include, for example, lemon, lime, orange, menthol and strawberry.

The crystal of the present invention may be prepared as a preparation for oral administration in accordance with a commonly known method, by, for example, compression-shaping it in the presence of an excipient, a disintegrant, a binder, a lubricant, or the like, and subsequently coating it as necessary by a commonly known method for the purpose of taste masking, enteric dissolution or sustained release. For an enteric preparation, an intermediate layer may be provided by a commonly known method between the enteric layer and the drug-containing layer for the purpose of separation of the two layers.

For preparing the crystal of the present invention as an orally disintegrating tablet, available methods include, for example, a method in which a core containing crystalline cellulose and lactose is coated with the crystal of the present invention and a basic inorganic salt, and is further coated with a coating layer containing a water-soluble polymer, to give a composition, which is coated with an enteric coating layer containing polyethylene glycol, further coated with an enteric coating layer containing triethyl citrate, still further coated with an enteric coating layer containing polyethylene glycol, and still yet further coated with mannitol, to give fine granules, which are mixed with additives and shaped. The above-mentioned "enteric coating layer" includes, for example, aqueous enteric polymer substrates such as cellu-

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lose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate, hydroxymethyl cellulose acetate succinate, methacrylic acid copolymers (e.g., Eudragit L30D-55 (trade name; produced by Rohm), Colicoat MAE30DP (trade name; produced by BASF), Polyquid PA30 (trade name; produced by San-yo Chemical)), carboxymethylethyl cellulose and shellac; sustained-release substrates such as methacrylic acid polymers (e.g., Eudragit NE30D (trade name), Eudragit RL30D (trade name), Eudragit RS30D (trade name), etc.); water-soluble polymers; plasticizers such as triethyl citrate, polyethylene glycol, acetylated monoglycerides, triacetin and castor oil; and mixtures thereof. The above-mentioned "additive" includes, for example, water-soluble sugar alcohols (e.g., sorbitol, mannitol, maltitol, reduced starch saccharides, xylitol, reduced palatinose, erythritol, etc.), crystalline cellulose (e.g., Ceolas KG 801, Avicel PH 101, Avicel PH 102, Avicel PH 301, Avicel PH 302, Avicel RC-591 (crystalline cellulose carmellose sodium)), low-substituted hydroxypropyl cellulose (e.g., LH-22, LH-32, LH-23, LH-33 (Shin-Etsu Chemical) and mixtures thereof); binders, souring agents, bubbling agents, sweetening agents, flavorings, lubricants, coloring agents, stabilizers, excipients, disintegrants etc. are also used.

The crystal of the present invention may be used in combination with 1 to 3 other active ingredients.

Such "other active ingredients" include, for example, anti-*Helicobacter pylori* activity substances, imidazole compounds, bismuth salts, quinolone compounds, and so forth. Of these substances, preferred are anti-*Helicobacter pylori* action substances, imidazole compounds etc. Such "anti-*Helicobacter pylori* action substances" include, for example, antibiotic penicillins (e.g., amoxicillin, benzylpenicillin, piperacillin, mecillinam, etc.), antibiotic cefems (e.g., cefixime, cefaclor, etc.), antibiotic macrolides (e.g., erythromycin, clarithromycin, etc.), antibiotic tetracyclines (e.g., tetracycline, minocycline, streptomycin, etc.), antibiotic aminoglycosides (e.g., gentamicin, amikacin, etc.), imipenem, and so forth. Of these substances, preferred are antibiotic penicillins, antibiotic macrolides etc. Such "imidazole compounds" include, for example, metronidazole, miconazole, etc. Such "bismuth salts" include, for example, bismuth acetate, bismuth citrate, etc. Such "quinolone compounds" include, for example, ofloxacin, ciprofloxacin, etc.

Such "other active ingredients" and the crystal of the present invention may also be used in combination as a mixture prepared as a single pharmaceutical composition [e.g., tablets, powders, granules, capsules (including soft capsules), liquids, injectable preparations, suppositories, sustained-release preparations, etc.], in accordance with a commonly known method, and may also be prepared as separate preparations and administered to the same subject simultaneously or at a time interval.

#### BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is hereinafter described in more detail by means of, but is not limited to, the following reference examples, examples and experimental examples.

In the following reference examples and examples, the term "room temperature" indicates about 15 to 30° C.

Melting points were measured using the Micro Melting Point Apparatus (produced by Yanagimoto Seisakusho), and uncorrected values are shown.

<sup>1</sup>H-NMR spectra were determined with CDCl<sub>3</sub> as the solvent using Varian Gemini-200; data are shown in chemical shift  $\delta$  (ppm) from the internal standard tetramethylsilane.

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IR was determined using SHIMADZU FTIR-8200.

UV was determined using the HITACHI U-3200 spectrophotometer.

Optical rotation  $[\alpha]_D$  was determined at 20° C. using the DIP-370 digital polarimeter (produced by JASCO).

Optical purity was determined by HPLC (column: CHIRALCEL OD 4.6 mm dia.×250 mm, temperature: about 20° C., mobilephase: hexane/2-propanol=80/20 or hexane/2-propanol=85/15, flow rate: 1.0 ml/min, detection wavelength: 285 nm) using a chiral column.

Crystal X-ray diffraction data for determining the absolute structure of sulfoxide were obtained by means of a 4-circle diffractometer (RIGAKU AFC5R) using the Cu-K $\alpha$  ray. After the initial phase was determined by the direct method, the fine structure was analyzed using SHELXL-93. X-ray powder diffraction was determined using the X-ray Powder Diffraction meter Rigaku RINT2500 (ultraX18) No. PX-3.

The other symbols used herein have the following definitions:

- s: singlet
- d: doublet
- t: triplet
- q: quartet
- m: multiplet
- bs: broad singlet
- J: binding constant

## EXAMPLES

### Reference Example 1

Isolation of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole)

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (lansoprazole) (racemate) (3.98 g) was dissolved in the following mobile phase (330 ml) and acetonitrile (37 ml) and fractionated by HPLC (column: CHIRALCEL OD 20 mm dia.×250 mm, temperature: 30° C., mobile phase: hexane/2-propanol/ethanol=255/35/10, flowrate: 16 ml/min, detection wavelength: 285 nm, 1 shot: 20–25 mg). Fractions of optical isomers of shorter retention time were combined and concentrated; the individual lots were combined and dissolved in ethanol and filtered through a 0.45  $\mu$ m filter; after hexane was added, the filtrate was again evaporated to dryness to yield R(+)-lansoprazole (1.6 g, optical purity>97.6%ee) as an amorphous substance.

The amorphous substance obtained was subjected to fractionation and isolation in the same manner as above to yield R(+)-lansoprazole (1.37 g, optical purity>99.9%ee) as an amorphous substance.

$[\alpha]_D=+174.3^\circ$ (c=0.994%, CHCl<sub>3</sub>)

### Reference Example 2

Isolation of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole)

Lansoprazole (racemate) (34.2 g) was dissolved in 2-propanol (1,710 ml) and hexane (1,140 ml) containing triethylamine (0.2%) and fractionated by HPLC (column: CHIRALCEL OD 50 mm dia. ×500 mm, temperature: room temperature, mobile phase: hexane/2-propanol=85/15, flow rate: 60 ml/min, detection wavelength: 285 nm, single injection: about 300 mg) to isolate the individual optical isomers. Fractions of an optical isomer of shorter retention time were combined and concentrated; the individual lots were combined and dissolved in ethanol (250 ml); after

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triethylamine (3 ml) was added, the solution was filtered through a 0.45  $\mu$ m filter. After the filtrate was concentrated, hexane was added, and the filtrate was again evaporated to dryness to yield R(+)-lansoprazole (9.31 g, optical purity 98.3%ee) as an amorphous substance.

### Reference Example 3

Production of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole)

In a nitrogen atmosphere, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]benzimidazole (20.0 g, 0.057 mol), toluene (100 ml), water (55 mg, 0.0031 mol as based on total water content) and diethyl (+)-tartrate (2.12 ml, 0.012 mol) were mixed and stirred at 50 to 55° C. for 30 minutes. After titanium (IV) isopropoxide (1.66 ml, 0.0057 mol) was added to the mixture in a nitrogen atmosphere, the mixture was stirred at 50 to 55° C. for 1 hour. After diisopropylethylamine (3.25 ml, 0.019 mol) was added to the resulting mixed liquor under cooling in a nitrogen atmosphere, cumene hydroperoxide (30.6 ml, content 82%, 0.17 mol) was added at 0 to 5° C., followed by 3.5 hours of stirring at 0 to 5° C., to cause the reaction.

Analysis of the reaction liquor by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfide at 1.32% and a sulfone at 1.81% as related substances in the reaction liquor, with no other related substances detected. The enantiomer excess rate of the title compound in said reaction liquor was 96.4%ee.

### Reference Example 4

Crystal of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole)

(1) In a nitrogen stream, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]benzimidazole (4.5 kg, 12.7 mol, containing 1.89 g of water), toluene (22 l), water (25 g, 1.39 mol, or 1.49 mol if based on total water content) and diethyl (+)-tartrate (0.958 l, 5.60 mol) were mixed. In a nitrogen stream, titanium (IV) isopropoxide (0.747 l, 2.53 mol) was added to this mixture at 50 to 60° C., and the mixture was stirred at the above temperature for 30 minutes. After diisopropylethylamine (0.733 l, 4.44 mol) was added to the resulting mixed liquor at room temperature in a nitrogen stream, cumene hydroperoxide (6.88 l, content 82%, 37.5 mol) was added at –5 to 5° C., followed by 1.5 hours of stirring at –5 to 5° C., to yield a reaction liquor.

Analysis of the reaction liquor by HPLC (column: Capcell Pak (Shiseido, Co. Ltd.), mobile phase: solvent mixture (acetonitrile/water/triethylamine=50/50/1); adjusted to. pH 7.0 with phosphoric acid, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfide at 1.87% and a sulfone at 1.59% as related substances in the reaction liquor, with no other related substances detected.

(2) To the reaction liquor obtained in (1) above, a 30% aqueous solution of sodium thiosulfate (17 l) was added, in a nitrogen stream, to decompose the residual cumene hydroperoxide. To the organic layer obtained by liquid separation, water (4.5 l), heptane (13.5 l), t-butyl methyl ether (18 l) and heptane (27 l) were added sequentially in this order, and this mixture was stirred to cause crystallization. The resulting crystal was separated and washed with t-butyl methyl ether-toluene (t-butyl methyl ether:toluene=4:1) (4 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffrac-



tion interplanar spacings (d) of 5.85, 4.70, 4.35, 3.66 and 3.48 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfone at 0.90% as a related substance in the crystal, with no sulfide or any other related substance detected. The (R)-lansoprazole enantiomer excess rate in this crystal was 100%ee.

(3) With stirring, a suspension in acetone (20 l) of 10 the wet crystal obtained in (2) above was added drop by drop into a mixed liquor of acetone (7 l) and water (34 l), then water (47 l) was added. The precipitated crystal was separated and washed with acetone-water (acetone:water=1:3) (4 l) and water (12 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100%ee.

(4) After the wet crystal obtained in (3) above was dissolved in ethyl acetate (45 l) and water (3 l), this solution was divided into liquid layers. The trace amount of insoluble matter in the organic layer was filtered off, then triethylamine (0.2 l) was added, after which the filtrate was concentrated under reduced pressure to a liquid volume of about 7 l. To this concentrate, methanol (2.3 l), about 12.5% aqueous ammonia at about 50° C. (23 l) and t-butyl methyl ether at about 50° C. (22 l) were added, and this liquid was divided into layers. To the organic layer, about 12.5% aqueous ammonia (11 l) was added, and this liquid was divided into layers (this operation was repeated once again). The water layers were combined, and ethyl acetate (22 l) was added, and then acetic acid was added drop by drop to reach a pH of about 8 under cooling. The liquid was divided into layers, and the water layer was extracted with ethyl acetate (11 l). The organic layers were combined and washed with about 20% saline (11 l). After triethylamine (0.2 l) was added, the organic layer was concentrated under reduced pressure. Acetone (5 l) was added to the concentrate, and this mixture was concentrated under reduced pressure. The concentrate was dissolved in acetone (9 l), and this solution was added drop by drop into a mixed liquor of acetone (4.5 l) and water (22.5 l), and then water (18 l) was added drop by drop to the mixed liquor obtained. The precipitated crystal was separated and washed sequentially with cold acetone-water (acetone:water=1:3) (3 l) and water (12 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100%ee.

(5) The wet crystal obtained in (4) above was dissolved in ethyl acetate (32 l). The water layer was separated by a

liquid separation procedure, and the organic layer obtained was concentrated under reduced pressure to a liquid volume of about 14 l. To the residual liquid, ethyl acetate (36 l) and activated charcoal (270 g) were added, after stirring, the activated charcoal was removed by filtration. The filtrate was concentrated under reduced pressure to a liquid volume of about 14 l. At about 40° C., heptane (90 l) was added drop by drop to the residual liquid. After stirring at the above temperature for about 30 minutes, the resulting crystal was separated, washed with about 40° C. ethyl acetate-heptane (ethyl acetate:heptane=1:8) (6 l), and dried to yield 3.4 kg of the title compound.

The results of powder X-ray diffraction analysis of this crystal are shown below.

The crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100%ee.

Example 1

Crystal of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole)

Amorphous R(+)-lansoprazole as obtained in Reference Example 1 (100 mg) was dissolved in acetonitrile (1 ml), which was gradually evaporated at room temperature in a nitrogen stream. After a crystal began to form, diethyl ether (1.5 ml) was added and the container was stoppered and kept standing at room temperature.

The crystal thus formed was subjected to X-ray structural analysis, and the absolute configuration of sulfoxide was found to be the R-configuration by a method using a Flack parameter. The remaining portion of the crystal was collected by filtration, twice washed with diethyl ether (1 ml), and dried under reduced pressure, to yield crystals of R(+)-lansoprazole (38 mg).

m.p.: 144.0–144.5° C. (dec.); Elemental analysis; Calculated: C: 52.03, H: 3.82, N: 11.38, S: 8.68, F: 15.43, O: 8.66; Found: C: 52.08, H: 3.76, N: 11.58, S: 8.75, F: 15.42; <sup>1</sup>H-NMR: 2.25 (3H, s), 4.40 (2H, q, J=7.8 Hz), 4.68 (1H, d, J=13.8 Hz), 4.85 (1H, d, J=13.8 Hz), 6.69 (1H, d, J=6.0 Hz), 7.29–7.39 (2H, m), 7.52 (1H, m), 7.81 (1H, m), 8.37 (1H, d, J=6.0 Hz), 11.00 (1H, bs). IR(v<sub>cm</sub><sup>-1</sup>): 3081, 3042, 2984, 1586, 1478, 1441, 1306, 1267, 1163. UVmax(CHCl<sub>3</sub>): 283.7 nm; [α]<sub>D</sub><sup>20</sup>=+199.2° (c=0.202%, CHCl<sub>3</sub>).

TABLE 1

Crystal Data and Structure Refinement Parameters	
Molecular formula:	C <sub>16</sub> H <sub>14</sub> N <sub>3</sub> O <sub>2</sub> F <sub>3</sub> S
Molecular weight:	369.36
Crystal color, habit:	Colorless, tabular
Crystal Dimension:	0.40 × 0.30 × 0.04 (mm)
Crystal system:	Monoclinic
Lattice constants:	a = 8.549(1) (Å) b = 23.350(1) (Å) c = 8.720(2) (Å) β 32 103.90(1) (°) v = 1,689.8(4) (Å <sup>3</sup> )
Space group:	P2 <sub>1</sub>
Z:	4
Density (calculated):	1.452 (g/cm <sup>3</sup> )

TABLE 1-continued

Crystal Data and Structure Refinement Parameters	
Effective reflection:	9.12
number/parameter number:	
R (I $\geq$ 2 $\sigma$ (I)):	0.036
Flack parameter:	-0.02(2)

Example 3

Crystal of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole)

Amorphous (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole as obtained in Reference Example 2 (9.17 g) was dissolved in acetone (20 ml) and water (15 ml) was added with gentle heating. After the solution was kept standing at room temperature overnight, water (20 ml) was added, followed by ultrasonication. After being collected by filtration, the solid was washed with water (30 ml, 20 ml), then washed with diisopropyl ether (20 ml), and dried under reduced pressure, to yield a solid (9.10 g). The solid obtained (9.00 g) was dissolved in acetone (30 ml), and after the solution was filtered, diisopropylether (50 ml) was added to the filtrate. A crystal seed was placed, and the mixture was kept standing at room temperature overnight. Precipitated crystals were collected by filtration, washed 3 times with diisopropyl ether (10 ml), and dried under reduced pressure, to yield crystals (7.85 g). The crystals obtained (7.80 g) were dissolved under heating in acetone (22.5 ml) and water (30 ml), and this solution was kept standing at room temperature for 1 hour. A precipitated solid was collected by filtration, washed with acetone-water (1:4) (15 ml), and dried under reduced pressure, to yield a solid (3.88 g). The solid obtained (3.88 g) was dissolved under heating in acetone (4 ml) and diisopropyl ether (14 ml) was added. This solution was kept standing at room temperature for 30 minutes. Precipitated crystals were collected by filtration, twice washed with diisopropyl ether (6 ml), and dried under reduced pressure, to yield crystals of R(+)-lansoprazole (3.40 g, optical purity 99.8%ee).

m.p.: 147.0–148.0° C. (dec.); Elemental analysis; Calculated: C: 52.03, H: 3.82, N: 11.38, S: 8.68, F: 15.43, O: 8.66; Found: C: 51.85, H: 3.92, N: 11.26, S: 8.82, F: 15.22; <sup>1</sup>H-NMR: 2.24 (3H, s), 4.38 (2H, q, J=7.8 Hz), 4.74 (1H, d, J=13.6 Hz), 4.87 (1H, d, J=13.6 Hz), 6.68 (1H, d, J=5.8 Hz), 7.26–7.36 (2H, m), 7.45(1H,m), 7.78 (1H, m), 8.35 (1H, d, J=5.8 Hz). IR(vcm<sup>-1</sup>): 3083, 3034, 2975, 1586, 1478, 1441, 1306, 1267, 1163; UVmax(CHCl<sub>3</sub>): 283.6 nm; [α]<sub>D</sub><sup>20</sup>=+180.3° (c=1.004%, CHCl<sub>3</sub>).

TABLE 2

X-ray Powder Diffraction Data			
2θ (°)	Half-value width	d-value (Å)	Relative intensity (%)
7.560	0.141	11.6841	100
13.060	0.165	6.7733	44
15.160	0.141	5.8394	55
15.440	0.141	5.7342	84
20.040	0.165	4.4271	23
21.720	0.165	4.0883	89
22.560	0.141	3.9380	24
22.820	0.141	3.8937	24
24.080	0.165	3.6927	37

TABLE 2-continued

X-ray Powder Diffraction Data			
2θ (°)	Half-value width	d-value (Å)	Relative intensity (%)
26.120	0.118	3.4088	32
28.680	0.165	3.1100	20

Example 3

Crystal of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole) 1.5 Hydrate

Amorphous (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole as obtained in Reference Example 1 (100 mg) was dissolved in ethanol (0.15 ml), and water. (0.15 ml) was added. After a seed was placed, the solution was kept standing at room temperature for 1 hour. Precipitated crystals were collected by filtration, twice washed with water (2 ml), and dried under reduced pressure, to yield crystals of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) 1.5 hydrate (96 mg).

m.p.: 76.0–80.0° C.; Elemental analysis; Calculated: C: 48.48, H: 4.32, N: 10.60, S: 8.09, F: 14.38, O: 14.13; Found: C: 48.52, H: 4.44, N: 10.49.

TABLE 3

X-ray Powder Diffraction Data			
2θ (°)	Half-value width	d-value (Å)	Relative intensity (%)
6.680	0.165	13.2212	9
9.200	0.165	9.6046	21
9.960	0.141	8.8734	25
10.980	0.165	8.0513	42
13.380	0.141	6.6120	22
14.960	0.141	5.9170	63
15.680	0.165	5.6469	100
17.640	0.212	5.0237	34
19.760	0.212	4.4892	33
25.420	0.188	3.5010	23
29.800	0.188	2.9957	20

Experimental Example 1

Suppressive action on gastric mucosal injury due to stress of water immersion restraint in rat.

Male SD rats (7 weeks of age, weighing 230 to 250 g) were fasted for 24 hours, after which they were stressed by being housed in restraint cages and immersed to below the xiphoid process in a standing position in a 23° C. constant-temperature water chamber. After 5 hours, the rats were removed from the cages and sacrificed using gaseous carbon dioxide, and their stomachs excised. After the lower portion of the esophagus was clipped, a 1% formalin solution (10 ml) was injected into the stomach via the duodenum, which was then occluded, and the stomach was immersed in the same solution. After 10 minutes, an incision was made along the greater curvature, and the length (mm) of each mucosal injury was measured under a stereomicroscope. The overall sum of the injury lengths in each stomach was taken as the gastric mucosal injury index.

The crystals of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) as obtained in Example 2 were suspended in 0.5% methyl cellulose (pH 9.5) containing 0.05 M NaHCO<sub>3</sub> and orally administered at 30

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minutes before stressing (dosing volume 2 ml/kg). Each treatment group comprised 9 animals. The control group (solvent administration group) and the drug administration group were compared by Steel's test.

The results are shown in Table 4.

TABLE 4

Sample	Dose (mg/kg)	Gastric mucosal injury index (mm)	Suppression rate (%)
Control	—	10.9 ± 1.9	—
(R)-lansoprazole crystal	3	0.2 ± 0.2*	98.0

Each figure of gastric mucosal injury index is the mean ± standard error for the 9 animals in each group.  
\*p < 0.01 (versus control group, Steel's test)

Experimental Example 2

The crystals of R (+)-lansoprazole as obtained in Example 2 (about 5 mg) and amorphous R(+)-lansoprazole as obtained in Reference Example 1 (about 5 mg) were each taken in a colorless glass bottle, and their stability during storage at 60° C. (stopper removed) was examined. A 25 ml solution (concentration: about 0.2 mg/ml) of the sample after completion of storage in the mobile phase, along with a standard solution prepared using the initial lot, was analyzed under the HPLC conditions shown below, and the R(+)-lansoprazole content (residual percentage) was calculated from the peak area obtained. The results are shown in Table 5.

HPLC analytical conditions	UV 275 nm
Detection wavelength:	
Column:	YMC Pro C18, 4.6 × 150 mm
Mobile phase:	Fluid prepared by adding phosphoric acid to water/acetonitrile/triethyl amine (63:37:1) to reach pH 7.
Flow rate:	1.0 ml/min
Column temperature:	40° C.
Sample injection volume:	10 µl

TABLE 5

Stability of R(+)-Lansoprazole Crystal and Amorphous			
Sample	Duration of storage	Description	Content (Residual percentage)
Crystal	1 week	Light-brown	97.0
	2 weeks	Brown	93.8
	4 weeks	Brown	91.7
Amorphous	1 week	Brown	70.8
	2 weeks	Blackish brown	57.5

When the sample was stored at 60° C. (exposed), the crystal of Example 2 retained a content exceeding 90% for up to 4 weeks, whereas the amorphous form of Reference Example 1 showed reduction in content to 70.8% after 1 week and 57.5% after 2 weeks. This finding demonstrates

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that the crystal of R(+)-lansoprazole is more stable and more preferable for use as a pharmaceutical etc. than the amorphous form.

INDUSTRIAL APPLICABILITY

The crystal of the present invention is useful as a pharmaceutical because it shows excellent antiulcer action, gastric acid secretion inhibiting action, mucosa-protecting action, anti-*Helicobacter pylori* action etc., and because it is of low toxicity. Furthermore, by crystallizing the (R)-isomer, not only its stability is improved but also its handling is facilitated so that it can be prepared as a solid pharmaceutical composition with good reproducibility. In addition, when orally administered, the crystal of the present invention is more absorbable and more rapidly shows its action than the racemate. In addition, when administered, the crystal of the present invention shows a higher Cmax and a greater AUC. than the racemate, and becomes less likely to be metabolized partly because of the increased protein-binding rate, thus showing an extended duration of action. The crystal of the present invention is therefore useful as a pharmaceutical of low dosage and with a low prevalence of adverse reactions.

What is claimed is:

1. A crystal of (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole wherein the X-ray powder diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.
2. A crystal of (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole 1.5 hydrate wherein the X-ray powder diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 13.22, 9.60, 8.87, 8.05, 6.61, 5.92, 5.65, 5.02, 4.49, 3.50 and 3.00 Angstrom.
3. A pharmaceutical composition which comprises the crystal according to claim 1 and a pharmaceutically acceptable excipient, carrier or diluent.
4. A pharmaceutical composition which comprises the crystal according to claim 2 and a pharmaceutically acceptable excipient, carrier or diluent.
5. A method for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer comprising formulating the composition with the crystal of claim 1.
6. A method for treating or preventing digestive ulcer in a mammal in need thereof which comprises administering to said mammal an effective amount of the crystal according to claim 1 with a pharmaceutically acceptable excipient, carrier or diluent.
7. A method for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer comprising formulating the composition with the crystal of claim 2.
8. A method for treating or preventing digestive ulcer in a mammal in need thereof which comprises administering to said mammal an effective amount of the crystal according to claim 2 with a pharmaceutically acceptable excipient, carrier or diluent.

\* \* \* \* \*

# **EXHIBIT B**



US006664276B2

(12) **United States Patent**  
**Fujishima et al.**

(10) **Patent No.:** **US 6,664,276 B2**  
(45) **Date of Patent:** **\*Dec. 16, 2003**

(54) **BENZIMIDAZOLE COMPOUND CRYSTAL**

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(73) Assignee: **Takeda Chemical Industries, Ltd.**, Osaka (JP)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/243,329**

(22) Filed: **Sep. 13, 2002**

(65) **Prior Publication Data**

US 2003/0045724 A1 Mar. 6, 2003

#### **Related U.S. Application Data**

(63) Continuation of application No. 09/674,624, filed as application No. PCT/JP00/03881 on Jun. 15, 2000, now Pat. No. 6,462,058.

(30) **Foreign Application Priority Data**

Jun. 17, 1999 (JP) ..... 11-171509

(51) **Int. Cl.**<sup>7</sup> ..... **C07D 401/12**; A61K 31/4439

(52) **U.S. Cl.** ..... **514/338**; 546/273.7

(58) **Field of Search** ..... 514/338; 546/273.7

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(57) **ABSTRACT**

A novel crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof of the present invention is useful for an excellent antiulcer agent.

**6 Claims, No Drawings**



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**BENZIMIDAZOLE COMPOUND CRYSTAL**

This application is a continuation of U.S. patent application Ser. No. 09/674,624 filed on Nov. 3, 2000, now issued U.S. Pat. No. 6,462,058, which application was the National Stage of International Application No. PCT/JP00/03881, filed on Jun. 15, 2000.

**DESCRIPTION****1. Technical Field**

The present invention relates to a crystal of a benzimidazole compound showing antiulcer action.

**2. Background Art**

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof having an antiulcer action is reported in JP-A-61-50978, etc.

There is a demand for a more stable and excellently absorbable antiulcer agent.

**DISCLOSURE OF INVENTION**

Having chiral sulfur in the molecular structure thereof, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole occurs in two kinds of optical isomers. After extensive exploration, the present inventors succeeded in optically resolving and crystallizing the (R)-isomer of 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, for the first time found that this crystal serves satisfactorily as a pharmaceutical, made further investigation based on this finding, and developed the present invention.

Accordingly, the present invention relates to:

- [1] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof;
- [2] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole;
- [3] a crystal according to the above [2] wherein the X-ray powder diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom;
- [4] a pharmaceutical composition which comprises the crystal according to the above [1];
- [5] a pharmaceutical composition according to the above [4], which is for treating or preventing digestive ulcer;
- [6] a method for treating or preventing digestive ulcer in a mammal in need thereof which comprises administering to said mammal an effective amount of the crystal according to the above [1] with a pharmaceutically acceptable excipient, carrier or diluent;
- [7] use of the crystal according to the above [1] for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer, and so forth.

The "salt" of "(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof" includes, for example, metal salts, salts with organic bases, salts with basic amino acids, and so forth. Preferred are physiologically acceptable salts.

Metal salts include, for example, alkali metal salts such as sodium salt and potassium salt; and alkaline earth metal salts such as calcium salt, magnesium salt and barium salt. Salts with organic bases include, for example, salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, etc. Salts with basic amino acids include, for example, salts with arginine, lysine, etc.

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The crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof may be a hydrate or not.

Said "hydrate" includes 0.5 hydrate to 5.0 hydrate. Among others, 0.5 hydrate, 1.0 hydrate, 1.5 hydrate, 2.0 hydrate and 2.5 hydrate are preferred. More preferred is 1.5 hydrate.

The crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof can be produced by subjecting 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof to an optical resolution or subjecting 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole to an asymmetrical oxidation to obtain the (R)-isomer, followed by crystallizing the resultant isomer.

Methods of optical resolution include per se known methods, for example, a fractional recrystallization method, a chiral column method, a diastereomer method, and so forth. Asymmetric oxidation includes per se known methods.

The "fractional recrystallization method" includes a method in which a salt is formed between a racemate and an optically active compound [e.g., (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine, etc.], which salt is separated by fractional recrystallization etc., and, if desired, subjected to a neutralization process, to give a free optical isomer.

The "chiral column method" includes a method in which a racemate or a salt thereof is applied to a column for optical isomer separation (chiral column). In the case of liquid chromatography, for example, optical isomers are separated by adding a racemate to a chiral column such as ENANTIO-OVM (produced by Tosoh Corporation) or the DAICEL CHIRAL series (produced by Daicel Corporation), and developing the racemate in water, a buffer (e.g., phosphate buffer), an organic solvent (e.g., hexane, ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, triethylamine, etc.), or a solvent mixture thereof. In the case of gas chromatography, for example, a chiral column such as CP-Chirasil-DeX CB (produced by GL Science) is used to separate optical isomers.

The "diastereomer method" includes a method in which a racemate and an optically active reagent are reacted (preferably, an optically active reagent is reacted to the 1-position of the benzimidazole group) to give a diastereomer mixture, which is then subjected to ordinary separation means (e.g., fractional recrystallization, chromatography, etc.) to obtain either diastereomer, which is subjected to a chemical reaction (e.g., acid hydrolysis, base hydrolysis, hydrogenolysis, etc.) to cut off the optically active reagent moiety, whereby the desired optical isomer is obtained. Said "optically active reagent" includes, for example, optically active organic acids such as MTPA [ $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic acid] and (-)-menthoxyacetic acid; and optically active alkoxymethyl halides such as (1R-endo)-2-(chloromethoxy)-1,3,3-trimethylbicyclo[2.2.1]heptane, etc.

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof is produced by the methods described in JP-A-61-50978, U.S. Pat. No. 4,628,098 etc. or analogous methods thereto.

Methods of crystallization includes per se known methods, for example, a crystallization from solution, a crystallization from vapor, and a crystallization from molten form.

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Methods of the "crystallization from solution" include, for example, a concentration method, a slow cooling method, a reaction method (diffusion method, electrolysis method), a hydrothermal growth method, a fusing agent method, and so forth. Solvents to be used include, for example, aromatic hydrocarbons (e.g., benzene, toluene, xylene, etc.), halogenated hydrocarbons (e.g., dichloromethane, chloroform, etc.), saturated hydrocarbons (e.g., hexane, heptane, cyclohexane, etc.), ethers (e.g., diethyl ether, dilsopropyl ether, tetrahydrofuran, dioxane, etc.), nitriles (e.g., acetonitrile, etc.), ketones (e.g., acetone, etc.), sulfoxides (e.g., dimethylsulfoxide, etc.), acid amides (e.g., N,N-dimethylformamide, etc.), esters (e.g., ethyl acetate, etc.), alcohols (e.g., methanol, ethanol, isopropyl alcohol, etc.), water, and so forth. These solvents may be used singly or in mixtures of two or more kinds in appropriate ratios (e.g., 1:1 to 1:100), ratios (e.g., 1:1 to 1:100).

Methods of the "crystallization from vapor" include, for example, a gasification method (sealed tube method, gas stream method), a gas phase reaction method, a chemical transportation method, and so forth.

Methods of the "crystallization from molten form" include, for example, a normal freezing method (pulling-up method, temperature gradient method, Bridgman method), a zone melting method (zone leveling method, float zone method), a special growth method (VLS method, liquid phase epitaxis method), and so forth.

For analyzing the crystal obtained, X-ray diffraction crystallographic analysis is commonly used. In addition, crystal orientation can also be determined by a mechanical method, an optical method, etc.

A thus-obtained crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof (hereinafter also referred to as "crystal of the present invention") is useful as a pharmaceutical because it shows excellent antiulcer action, gastric acid secretion-inhibiting action, mucosa-protecting action, anti-*Helicobacter pylori* action, etc., and because it is of low toxicity. Furthermore, by crystallizing the (R)-isomer, not only its stability is improved but also its handling is facilitated so that it can be prepared as a solid pharmaceutical composition with good reproducibility. In addition, when orally administered, the crystal of the present invention is more absorbable and more rapidly shows its action than the racemate. In addition, when administered, the crystal of the present invention shows a higher C<sub>max</sub> (maximum blood concentration) and a greater AUC (area under the concentration-time curve) than the racemate, and becomes less likely to be metabolized partly because of the increased protein-binding rate, thus showing an extended duration of action. The crystal of the present invention is therefore useful as a pharmaceutical of low dosage and with a low prevalence of adverse reactions.

The crystal of the present invention is useful in mammals (e.g., humans, monkeys, sheep, bovines, horses, dogs, cats, rabbits, rats, mice, etc.) for the treatment and prevention of digestive ulcer (e.g., gastric ulcer, duodenal ulcer, stomal ulcer, Zollinger-Ellison syndrome, etc.), gastritis, reflux esophagitis, NUD (non-ulcer dyspepsia), gastric cancer and gastric MALT lymphoma; *Helicobacter pylori* eradication; suppression of upper gastrointestinal hemorrhage due to digestive ulcer, acute stress ulcer and hemorrhagic gastritis; suppression of upper gastrointestinal hemorrhage due to invasive stress (stress from major surgery necessitating intensive management after surgery, and from cerebral vascular disorder, head trauma, multiple organ failure and extensive burns necessitating intensive treatment); treatment

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and prevention of ulcer caused by a nonsteroidal anti-inflammatory agent; treatment and prevention of hyperacidity and ulcer due to postoperative stress; pre-anesthetic administration etc.

The crystal of the present invention is of low toxicity and can be safely administered orally or non-orally (e.g., topical, rectal and intravenous administration, etc.), as such or in the form of pharmaceutical compositions formulated with a pharmacologically acceptable carrier, e.g., tablets (including sugar-coated tablets and film-coated tablets), powders, granules, capsules (including soft capsules), orally disintegrating tablets, liquids, injectable preparations, suppositories, sustained-release preparations and patches, in accordance with a commonly known method.

The content of the crystal of the present invention in the pharmaceutical composition of the present invention is about 0.01 to 100% by weight relative to the entire composition. Varying depending on subject of administration, route of administration, target disease etc., its dose is normally about 0.5 to 1,500 mg/day, preferably about 5 to 150 mg/day, based on the active ingredient, for example, when it is orally administered as an antiulcer agent to an adult human (60 kg). The crystal of the present invention may be administered once daily or in 2 to 3 divided portions per day.

Pharmacologically acceptable carriers that may be used to produce the pharmaceutical composition of the present invention include various organic or inorganic carrier substances in common use as pharmaceutical materials, including excipients, lubricants, binders, disintegrants, water-soluble polymers and basic inorganic salts for solid preparations; and solvents, dissolution aids, suspending agents, isotonicizing agents, buffers and soothing agents for liquid preparations. Other ordinary pharmaceutical additives such as preservatives, antioxidants, coloring agents, sweetening agents, souring agents, bubbling agents and flavorings may also be used as necessary.

Such "excipients" include, for example, lactose, sucrose, D-mannitol, starch, cornstarch, crystalline cellulose, light silicic anhydride and titanium oxide.

Such "lubricants" include, for example, magnesium stearate, sucrose fatty acid esters, polyethylene glycol, talc and stearic acid.

Such "binders" include, for example, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, crystalline cellulose,  $\alpha$ -starch, polyvinylpyrrolidone, gum arabic powder, gelatin, pullulan and low-substitutional hydroxypropyl cellulose.

Such "disintegrants" include (1) crosslinked povidone, (2) what is called super-disintegrants such as crosslinked carmellose sodium (FMC-Asahi Chemical) and carmellose calcium (Gotoku Yakuhin), (3) carboxymethyl starch sodium (e.g., product of Matsutani Chemical), (4) low-substituted hydroxypropyl cellulose (e.g., product of Shin-Etsu Chemical), (5) cornstarch, and so forth. Said "crosslinked povidone" may be any crosslinked polymer having the chemical name 1-ethenyl-2-pyrrolidinone homopolymer, including polyvinylpyrrolidone (PVPP) and 1-vinyl-2-pyrrolidinone homopolymer, and is exemplified by Colidon CL (produced by BASF), Polyplasdon XL (produced by ISP), Polyplasdon XL-10 (produced by ISP) and Polyplasdon INF-10 (produced by ISP).

Such "water-soluble polymers" include, for example, ethanol-soluble water-soluble polymers [e.g., cellulose derivatives such as hydroxypropyl cellulose (hereinafter also referred to as HPC), polyvinylpyrrolidone] and ethanol-insoluble water-soluble polymers [e.g., cellulose derivatives such as hydroxypropylmethyl cellulose (hereinafter also

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referred to as HPMC), methyl cellulose and carboxymethyl cellulose sodium, sodium polyacrylate, polyvinyl alcohol, sodium alginate, guar gum].

Such "basic inorganic salts" include, for example, basic inorganic salts of sodium, potassium, magnesium and/or calcium. Preferred are basic inorganic salts of magnesium and/or calcium. More preferred are basic inorganic salts of magnesium. Such basic inorganic salts of sodium include, for example, sodium carbonate, sodium hydrogen carbonate, disodium hydrogenphosphate, etc. Such basic inorganic salts of potassium include, for example, potassium carbonate, potassium hydrogen carbonate, etc. Such basic inorganic salts of magnesium include, for example, heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite  $[Mg_6Al_2(OH)_{16}CO_3 \cdot 4H_2O]$ , alumina hydroxide magnesium, and so forth. Among others, preferred is heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, etc. Such basic inorganic salts of calcium include, for example, precipitated calcium carbonate, calcium hydroxide, etc.

Such "solvents" include, for example, water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil and olive oil.

Such "dissolution aids" include, for example, polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate and sodium citrate.

Such "suspending agents" include, for example, surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and monostearic glycerol; and hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose.

Such "isotonizing agents" include, for example, glucose, D-sorbitol, sodium chloride, glycerol and D-mannitol.

Such "buffers" include, for example, buffer solutions of phosphates, acetates, carbonates, citrates etc.

Such "soothing agents" include, for example, benzyl alcohol.

Such "preservatives" include, for example, p-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid.

Such "antioxidants" include, for example, sulfites, ascorbic acid and  $\alpha$ -tocopherol.

Such "coloring agents" include, for example, food colors such as Food Color Yellow No. 5, Food Color Red No. 2 and Food Color Blue No. 2; and food lake colors and red oxide.

Such "sweetening agents" include, for example, saccharin sodium, dipotassium glycyrrhetinate, aspartame, stevia and thaumatin.

Such "souring agents" include, for example, citric acid (citric anhydride), tartaric acid and malic acid.

Such "bubbling agents" include, for example, sodium bicarbonate.

Such "flavorings" may be synthetic substances or naturally occurring substances, and include, for example, lemon, lime, orange, menthol and strawberry.

The crystal of the present invention may be prepared as a preparation for oral administration in accordance with a commonly known method, by, for example, compression-shaping it in the presence of an excipient, a disintegrant, a binder, a lubricant, or the like, and subsequently coating it as necessary by a commonly known method for the purpose of

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taste masking, enteric dissolution or sustained release. For an enteric preparation, an intermediate layer may be provided by a commonly known method between the enteric layer and the drug-containing layer for the purpose of separation of the two layers.

For preparing the crystal of the present invention as an orally disintegrating tablet, available methods include, for example, a method in which a core containing crystalline cellulose and lactose is coated with the crystal of the present invention and a basic inorganic salt, and is further coated with a coating layer containing a water-soluble polymer, to give a composition, which is coated with an enteric coating layer containing polyethylene glycol, further coated with an enteric coating layer containing triethyl citrate, still further coated with an enteric coating layer containing polyethylene glycol, and still yet further coated with mannitol, to give fine granules, which are mixed with additives and shaped. The above-mentioned "enteric coating layer" includes, for example, aqueous enteric polymer substrates such as cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate, hydroxymethyl cellulose acetate succinate, methacrylic acid copolymers (e.g., Eudragit L30D-55 (trade name); produced by Rohm), Colicoat MAE30DP (trade name); produced by BASF), Polyquid PA30 (trade name; produced by San-yo Chemical)), carboxymethylethyl cellulose and shellac; sustained-release substrates such as methacrylic acid polymers (e.g., Eudragit NE30 D (trade name), Eudragit RL30D (trade name), Eudragit RS30D (trade name), etc.); water-soluble polymers; plasticizers such as triethyl citrate, polyethylene glycol, acetylated monoglycerides, triacetin and castor oil; and mixtures thereof. The above-mentioned "additive" includes, for example, water-soluble sugar alcohols (e.g., sorbitol, mannitol, maltitol, reduced starch saccharides, xylitol, reduced palatinose, erythritol, etc.), crystalline cellulose (e.g., Ceolas KG 801, Avicel PH 101, Avicel PH 102, Avicel PH 301, Avicel PH 302, Avicel RC-591 (crystalline cellulose carmellose sodium)), low-substituted hydroxypropyl cellulose (e.g., LH-22, LH-32, LH-23, LH-33 (Shin-Etsu Chemical) and mixtures thereof); binders, souring agents, bubbling agents, sweetening agents, flavorings, lubricants, coloring agents, stabilizers, excipients, disintegrants etc. are also used.

The crystal of the present invention may be used in combination with 1 to 3 other active ingredients.

Such "other active ingredients" include, for example, anti-*Helicobacter pylori* activity substances, imidazole compounds, bismuth salts, quinolone compounds, and so forth. Of these substances, preferred are anti-*Helicobacter pylori* action substances, imidazole compounds etc. Such "anti-*Helicobacter pylori* action substances" include, for example, antibiotic penicillins (e.g., amoxicillin, benzylpenicillin, piperacillin, mecillinam, etc.), antibiotic cefems (e.g., cefixime, cefaclor, etc.), antibiotic macrolides (e.g., erythromycin, clarithromycin, etc.), antibiotic tetracyclines (e.g., tetracycline, minocycline, streptomycin, etc.), antibiotic aminoglycosides (e.g., gentamicin, amikacin, etc.), imipenem and so forth. Of these substances, preferred are antibiotic penicillins, antibiotic macrolides etc. Such "imidazole compounds" include, for example, metronidazole, miconazole, etc. Such "bismuth salts" include, for example, bismuth acetate, bismuth citrate, etc. Such "quinolone compounds" include, for example, ofloxacin, ciprofloxacin, etc.

Such "other active ingredients" and the crystal of the present invention may also be used in combination as a mixture prepared as a single pharmaceutical composition



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[e.g., tablets, powders, granules, capsules (including soft capsules), liquids, injectable preparations, suppositories, sustained-release preparations, etc.], in accordance with a commonly known method, and may also be prepared as separate preparations and administered to the same subject simultaneously or at a time interval.

#### BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is hereinafter described in more detail by means of, but is not limited to, the following reference examples, examples and experimental examples.

In the following reference examples and examples, the term "room temperature" indicates about 15 to 30 °C.

Melting points were measured using the Micro Melting Point Apparatus (produced by Yanagimoto Seisakusho), and uncorrected values are shown.

<sup>1</sup>H-NMR spectra were determined with CDCl<sub>3</sub> as the solvent using Varian Gemini-200; data are shown in chemical shift  $\delta$  (ppm) from the internal standard tetramethylsilane.

IR was determined using SHIMADZU FTIR-8200.

UV was determined using the HITACHI U-3200 spectrophotometer.

Optical rotation  $[\alpha]_D$  was determined at 20° C. using the DIP-370 digital polarimeter (produced by JASCO).

Optical purity was determined by HPLC (column: CHIRALCEL OD 4.6mm dia.x250 mm, temperature: about 20° C., mobile phase: hexane/2-propanol=80/20 or hexane/2-propanol=85/15, flow rate: 1.0 ml/min, detection wavelength: 285nm) using a chiral column.

Crystal X-ray diffraction data for determining the absolute structure of sulfoxide were obtained by means of a 4-circle diffractometer (RIGAKU AFC5R) using the Cu-K $\alpha$  ray. After the initial phase was determined by the direct method, the fine structure was analyzed using SHELXL-93. X-ray powder diffraction was determined using the X-ray Powder Diffraction meter Rigaku RINT2500 (ultraX18) No. PX-3.

The other symbols used herein have the following definitions:

s: singlet  
d: doublet  
t: triplet  
q: quartet  
m: multiplet  
bs: broad singlet  
J: binding constant

#### EXAMPLES

##### Reference Example 1

Isolation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (lansoprazole) (racemate) (3.98 g) was dissolved in the following mobile phase (330 ml) and acetonitrile (37 ml) and fractionated by HPLC (column: CHIRALCEL OD 20 mm dia.x250 mm, temperature: 30° C., mobile phase: hexane/2-propanol/ethanol=255/35/10, flowrate: 16 ml/min, detection wavelength: 285 nm, 1 shot: 20–25 mg). Fractions of optical

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isomers of shorter retention time were combined and concentrated; the individual lots were combined and dissolved in ethanol and filtered through a 0.45  $\mu$ m filter; after hexane was added, the filtrate was again evaporated to dryness to yield R(+)-lansoprazole (1.6 g, optical purity>97.6% ee) as an amorphous substance.

The amorphous substance obtained was subjected to fractionation and isolation in the same manner as above to yield R(+)-lansoprazole (1.37 g, optical purity>99.9% ee) as an amorphous substance.

$[\alpha]_D^{20}=+174.3^\circ$  ( $c=0.994\%$ , CHCl<sub>3</sub>)

##### Reference Example 2

Isolation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

Lansoprazole (racemate) (34.2 g) was dissolved in 2-propanol (1,710 ml) and hexane (1,140 ml) containing triethylamine (0.2%) and fractionated by HPLC (column: CHIRALCEL OD 50 mm dia.x500 mm, temperature: room temperature, mobile phase: hexane/2-propanol=85/15, flow rate: 60 ml/min, detection wavelength: 285 nm, single injection: about 300 mg) to isolate the individual optical isomers. Fractions of an optical isomer of shorter retention time were combined and concentrated; the individual lots were combined and dissolved in ethanol (250 ml); after triethylamine (3 ml) was added, the solution was filtered through a 0.45  $\mu$ m filter. After the filtrate was concentrated, hexane was added, and the filtrate was again evaporated to dryness to yield R(+)-lansoprazole (9.31 g, optical purity 98.3% ee) as an amorphous substance.

##### Reference Example 3

Production of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

In a nitrogen atmosphere, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]benzimidazole (20.0 g, 0.057 mol), toluene (100 ml), water (55 mg, 0.0031 mol as based on total water content) and diethyl (+)-tartrate (2.12 ml, 0.012 mol) were mixed and stirred at 50 to 55° C. for 30 minutes. After titanium (IV) isopropoxide (1.66 ml, 0.0057 mol) was added to the mixture in a nitrogen atmosphere, the mixture was stirred at 50 to 55° C. for 1 hour. After diisopropylethylamine (3.25 ml, 0.019 mol) was added to the resulting mixed liquor under cooling in a nitrogen atmosphere, cumene hydroperoxide (30.6 ml, content 82%, 0.17 mol) was added at 0 to 5° C., followed by 3.5 hours of stirring at 0 to 5° C., to cause the reaction.

Analysis of the reaction liquor by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfide at 1.32% and a sulfone at 1.81% as related substances in the reaction liquor, with no other related substances detected. The enantiomer excess rate of the title compound in said reaction liquor was 96.4% ee.

##### Reference Example 4

Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

(1) In a nitrogen stream, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]benzimidazole (4.5

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kg, 12.7 mol, containing 1.89 g of water), toluene (22 l), water (25 g, 1.39 mol, or 1.49 mol if based on total water content) and diethyl (+)-tartrate (0.958 l, 5.60 mol) were mixed. In a nitrogen stream, titanium (IV) isopropoxide (0.747 l, 2.53 mol) was added to this mixture at 50 to 60° C., and the mixture was stirred at the above temperature for 30 minutes. After diisopropylethylamine (0.733 l, 4.44 mol) was added to the resulting mixed liquor at room temperature in a nitrogen stream, cumene hydroperoxide (6.88 l, content 82%, 37.5 mol) was added at -5 to 5° C., followed by 1.5 hours of stirring at -5 to 5° C., to yield a reaction liquor.

Analysis of the reaction liquor by HPLC (column: Capcell Pak (Shiseido, Co. Ltd.), mobile phase: solvent mixture (acetonitrile/water/ triethylamine=50/50/1); adjusted to pH 7.0 with phosphoric acid, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfide at 1.87% and a sulfone at 1.59% as related substances in the reaction liquor, with no other related substances detected.

(2) To the reaction liquor obtained in (1) above, a 30% aqueous solution of sodium thiosulfate (17 l) was added, in a nitrogen stream, to decompose the residual cumene hydroperoxide. To the organic layer obtained by liquid separation, water (4.5 l), heptane (13.5 l), t-butyl methyl ether (18 l) and heptane (27 l) were added sequentially in this order, and this mixture was stirred to cause crystallization. The resulting crystal was separated and washed with t-butyl methyl ether-toluene (t-butyl methyl ether:toluene=4:1) (4 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 5.85, 4.70, 4.35, 3.66 and 3.48 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfone at 0.90% as a related substance in the crystal, with no sulfide or any other related substance detected. The (R)-lansoprazole enantiomer excess rate in this crystal was 100% ee.

(3) With stirring, a suspension in acetone (20 l) of the wet crystal obtained in (2) above was added drop by drop into a mixed liquor of acetone (7 l) and water (34 l), then water (47 l) was added. The precipitated crystal was separated and washed with acetone-water (acetone:water=1:3) (4 l) and water (12 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100% ee.

(4) After the wet crystal obtained in (3) above was dissolved in ethyl acetate (45 l) and water (3 l), this solution was divided into liquid layers. The trace amount of insoluble

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matter in the organic layer was filtered off, then triethylamine (0.2 l) was added, after which the filtrate was concentrated under reduced pressure to a liquid volume of about 7 l. To this concentrate, methanol (2.3 l), about 12.5% aqueous ammonia at about 50° C. (23 l) and t-butyl methyl ether at about 50° C. (22 l) were added, and this liquid was divided into layers. To the organic layer, about 12.5% aqueous ammonia (11 l) was added, and this liquid was divided into layers (this operation was repeated once again). The water layers were combined, and ethyl acetate (22 l) was added, and then acetic acid was added drop by drop to reach a pH of about 8 under cooling. The liquid was divided into layers, and the water layer was extracted with ethyl acetate (11 l). The organic layers were combined and washed with about 20% saline (11 l). After triethylamine (0.2 l) was added, the organic layer was concentrated under reduced pressure. Acetone (5 l) was added to the concentrate, and this mixture was concentrated under reduced pressure. The concentrate was dissolved in acetone (9 l), and this solution was added drop by drop into a mixed liquor of acetone (4.5 l) and water (22.5 l), and then water (18 l) was added drop by drop to the mixed liquor obtained. The precipitated crystal was separated and washed sequentially with cold acetone-water (acetone:water=1:3) (3 l) and water (12 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100% ee.

(5) The wet crystal obtained in (4) above was dissolved in ethyl acetate (32 l). The water layer was separated by a liquid separation procedure, and the organic layer obtained was concentrated under reduced pressure to a liquid volume of about 14 l. To the residual liquid, ethyl acetate (36 l) and activated charcoal (270 g) were added, after stirring, the activated charcoal was removed by filtration. The filtrate was concentrated under reduced pressure to a liquid volume of about 14 l. At about 40° C., heptane (90 l) was added drop by drop to the residual liquid. After stirring at the above temperature for about 30 minutes, the resulting crystal was separated, washed with about 40° C. ethyl acetate-heptane (ethyl acetate:heptane=1:8) (6 l), and dried to yield 3.4 kg of the title compound.

The results of powder X-ray diffraction analysis of this crystal are shown below.

The crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100% ee.

#### Example 1

Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

Amorphous R(+)-lansoprazole as obtained in Reference Example 1 (100 mg) was dissolved in acetonitrile (1 ml),

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which was gradually evaporated at room temperature in a nitrogen stream. After a crystal began to form, diethyl ether (1.5 ml) was added and the container was stoppered and kept standing at room temperature.

The crystal thus formed was subjected to X-ray structural analysis, and the absolute configuration of sulfoxide was found to be the R-configuration by a method using a Flack parameter. The remaining portion of the crystal was collected by filtration, twice washed with diethyl ether (1 ml), and dried under reduced pressure, to yield crystals of R(+)-lansoprazole (38 mg).

m.p.: 144.0–144.5° C. (dec.)

## Elemental Analysis

Calculated: C: 52.03, H: 3.82, N: 11.38, S: 8.68, F: 15.43, O: 8.66 Found: C: 52.08, H: 3.76, N: 11.58, S: 8.75, F: 15.42

<sup>1</sup>H-NMR: 2.25(3H,s), 4.40(2H,q,J=7.8 Hz), 4.68(1H,d,J=13.8 Hz), 4.85(1H,d,J=13.8 Hz), 6.69(1H,d,J=6.0 Hz), 7.29–7.39(2H,m), 7.52(1H,m), 7.81(1H,m), 8.37(1H,d,J=6.0 Hz), 11.00(1H,bs). IR (ν cm<sup>-1</sup>): 3081, 3042, 2984, 1586, 1478, 1441, 1306, 1267, 1163.

UVmax (CHCl<sub>3</sub>): 283.7 nm

[α]<sub>D</sub><sup>20</sup> = +199.2° (c=0.202%, CHCl<sub>3</sub>)

TABLE 1

Crystal Data and Structure Refinement Parameters	
Molecular formula	C <sub>16</sub> H <sub>14</sub> N <sub>3</sub> O <sub>2</sub> F <sub>3</sub> S
Molecular weight	369.36
Crystal color, habit	Colorless, tabular
Crystal Dimension	0.40 × 0.30 × 0.04 (mm)
Crystal system	Monoclinic
Lattice constants	a = 8.549(1) (Å) b = 23.350(1) (Å) c = 8.720(2) (Å) β = 103.90(1) (°) V = 1,689.8(4) (Å <sup>3</sup> )
Space group	P2 <sub>1</sub>
Z	4
Density (calculated)	1.452 (g/cm <sup>3</sup> )
Effective reflection	9.12
number/parameter number	
R (I ≥ 2σ(I))	0.036
Flack parameter	−0.02(2)

## Example 2

Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

Amorphous (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole as obtained in Reference Example 2 (9.17 g) was dissolved in acetone (20 ml), and water (15 ml) was added with gentle heating. After the solution was kept standing at room temperature overnight, water (20 ml) was added, followed by ultrasonication. After being collected by filtration, the solid was washed with water (30 ml, 20 ml), then washed with diisopropyl ether (20 ml), and dried under reduced pressure, to yield a solid (9.10 g). The solid obtained (9.00 g) was dissolved in acetone (30 ml), and after the solution was filtered, diisopropyl ether (50 ml) was added to the filtrate. A crystal seed was placed, and the mixture was kept standing at room temperature overnight. Precipitated crystals were collected by filtration, washed 3 times with diisopropyl ether (10 ml), and dried under reduced pressure, to yield crystals (7.85 g). The crystals obtained (7.80 g) were dissolved under

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heating in acetone (22.5 ml) and water (30 ml), and this solution was kept standing at room temperature for 1 hour. A precipitated solid was collected by filtration, washed with acetone-water (1:4) (15 ml), and dried under reduced pressure, to yield a solid (3.88 g). The solid obtained (3.88 g) was dissolved under heating in acetone (4 ml) and diisopropyl ether (14 ml) was added. This solution was kept standing at room temperature for 30 minutes. Precipitated crystals were collected by filtration, twice washed with diisopropyl ether (6 ml), and dried under reduced pressure, to yield crystals of R(+)-lansoprazole (3.40 g, optical purity 99.8% ee).

m.p.: 147.0–148.0° C. (dec.)

## Elemental Analysis

Calculated: C: 52.03, H: 3.82, N: 11.38, S: 8.68, F: 15.43, O: 8.66

Found: C: 51.85, H: 3.92, N: 11.26, S: 8.82, F: 15.22

<sup>1</sup>H-NMR: 2.24(3H,s), 4.38(2H,q,J=7.8 Hz), 4.74(1H,d,J=13.6 Hz), 4.87(1H,d,J=13.6 Hz), 6.68(1H,d,J=5.8 Hz), 7.26–7.36(2H,m), 7.45(1H,m), 7.78(1H,m), 8.35(1H,d,J=5.8 Hz).

IR (ν cm<sup>-1</sup>): 3083, 3034, 2975, 1586, 1478, 1441, 1306, 1267, 1163

UVmax (CHCl<sub>3</sub>): 283.6 nm

[α]<sub>D</sub><sup>20</sup> = +180.3° (c=1.004%, CHCl<sub>3</sub>)

TABLE 2

X-ray Powder Diffraction Data			
2θ (°)	Half-value width	d-value (Å)	Relative intensity (%)
7.560	0.141	11.6841	100
13.060	0.165	6.7733	44
15.160	0.141	5.8394	55
15.440	0.141	5.7342	84
20.040	0.165	4.4271	23
21.720	0.165	4.0883	89
22.560	0.141	3.9380	24
22.820	0.141	3.8937	24
24.080	0.165	3.6927	37
26.120	0.118	3.4088	32
28.680	0.165	3.1100	20

## Example 3

Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) 1.5 hydrate

Amorphous (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole as obtained in Reference Example 1 (100 mg) was dissolved in ethanol (0.15 ml), and water (0.15 ml) was added.

After a seed was placed, the solution was kept standing at room temperature for 1 hour. Precipitated crystals were collected by filtration, twice washed with water (2 ml), and dried under reduced pressure, to yield crystals of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) 1.5 hydrate (96 mg).

m.p.: 76.0–80.0° C.

## Elemental Analysis

Calculated: C: 48.48, H: 4.32, N: 10.60, S: 8.09, F: 14.38, O: 14.13 Found: C: 48.52, H: 4.44, N: 10.49

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TABLE 3

X-ray Powder Diffraction Data			
2 $\theta$ (°)	Half-value width	d-value (Å)	Relative intensity (%)
6.680	0.165	13.2212	9
9.200	0.165	9.6046	21
9.960	0.141	8.8734	25
10.980	0.165	8.0513	42
13.380	0.141	6.6120	22
14.960	0.141	5.9170	63
15.680	0.165	5.6469	100
17.640	0.212	5.0237	34
19.760	0.212	4.4892	33
25.420	0.188	3.5010	23
29.800	0.188	2.9957	20

## Experimental Example 1

Suppressive action on gastric mucosal injury due to stress of water immersion restraint in rat

Male SD rats (7 weeks of age, weighing 230 to 250 g) were fasted for 24 hours, after which they were stressed by being housed in restraint cages and immersed to below the xiphoid process in a standing position in a 23° C. constant-temperature water chamber. After 5 hours, the rats were removed from the cages and sacrificed using gaseous carbon dioxide, and their stomachs excised. After the lower portion of the esophagus was clipped, a 1% formalin solution (10 ml) was injected into the stomach via the duodenum, which was then occluded, and the stomach was immersed in the same solution. After 10 minutes, an incision was made along the greater curvature, and the length (mm) of each mucosal injury was measured under a stereomicroscope. The overall sum of the injury lengths in each stomach was taken as the gastric mucosal injury index.

The crystals of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) as obtained in Example 2 were suspended in 0.5% methyl cellulose (pH 9.5) containing 0.05 M NaHCO<sub>3</sub> and orally administered at 30 minutes before stressing (dosing volume 2 ml/kg). Each treatment group comprised 9 animals. The control group (solvent administration group) and the drug administration group were compared by Steel's test.

The results are shown in Table 4.

TABLE 4

Sample	Dose (mg/kg)	Gastric mucosal injury index (mm)	Suppression rate (%)
Control	—	10.9 ± 1.9	—
(R)-lansoprazole crystal	3	0.2 ± 0.2*	98.0

Each figure of gastric mucosal injury index is the mean ± standard error for the 9 animals in each group.

\*p < 0.01 (versus control group, Steel's test)

## Experimental Example 2

The crystals of R(+)-lansoprazole as obtained in Example 2 (about 5 mg) and amorphous R(+)-lansoprazole as obtained in Reference Example 1 (about 5 mg) were each taken in a colorless glass bottle, and their stability during storage at 60° C. (stopper removed) was examined. A 25 ml solution (concentration: about 0.2 mg/ml) of the sample after completion of storage in the mobile phase, along with

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a standard solution prepared using the initial lot, was analyzed under the HPLC conditions shown below, and the R(+)-lansoprazole content (residual percentage) was calculated from the peak area obtained. The results are shown in Table 5.

HPLC analytical conditions

Detection wavelength	UV 275 nm
Column	YMC Pro C18, 4.6 × 150 mm
Mobile phase	Fluid prepared by adding phosphoric acid to water/acetonitrile/triethylamine (63:37:1) to reach pH 7.
Flow rate	1.0 ml/min
Column temperature	40° C.
Sample injection volume	10 $\mu$ l

TABLE 5

Stability of R(+)-Lansoprazole Crystal and Amorphous

Sample	Duration of storage	Description	Content (Residual percentage)
Crystal	1 week	Light-brown	97.0
	2 weeks	Brown	93.8
	4 weeks	Brown	91.7
Amorphous	1 week	Brown	70.8
	2 weeks	Blackish brown	57.5

When the sample was stored at 60° C. (exposed), the crystal of Example 2 retained a content exceeding 90% for up to 4 weeks, whereas the amorphous form of Reference Example 1 showed reduction in content to 70.8% after 1 week and 57.5% after 2 weeks. This finding demonstrates that the crystal of R(+)-lansoprazole is more stable and more preferable for use as a pharmaceutical etc. than the amorphous form.

## Industrial Applicability

The crystal of the present invention is useful as a pharmaceutical because it shows excellent antiulcer action, gastric acid secretion-inhibiting action, mucosa-protecting action, anti-*Helicobacter pylori* action etc., and because it is of low toxicity. Furthermore, by crystallizing the (R)-isomer, not only its stability is improved but also its handling is facilitated so that it can be prepared as a solid pharmaceutical composition with good reproducibility. In addition, when orally administered, the crystal of the present invention is more absorbable and more rapidly shows its action than the racemate. In addition, when administered, the crystal of the present invention shows a higher C<sub>max</sub> and a greater AUC than the racemate, and becomes less likely to be metabolized partly because of the increased protein-binding rate, thus showing an extended duration of action. The crystal of the present invention is therefore useful as a pharmaceutical of low dosage and with a low prevalence of adverse reactions.

What is claimed is:

1. A crystalline compound of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof.

2. A crystalline compound of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole.

3. A pharmaceutical composition comprising:

a crystalline compound of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof; and

a pharmaceutically acceptable excipient, carrier or diluent.



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4. A pharmaceutical composition according to claim 3, which is for treating or preventing digestive ulcer.

5. A method for treating or preventing digestive ulcer in a mammal in need thereof which comprises administering to said mammal an effective amount of a crystalline compound of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof.

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6. A method for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer comprising formulating the composition with a crystalline compound of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof.

\* \* \* \* \*

# **EXHIBIT C**



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(12) **United States Patent**  
**Fujishima et al.**(10) **Patent No.:** **US 6,939,971 B2**  
(45) **Date of Patent:** **\*Sep. 6, 2005**(54) **BENZIMIDAZOLE COMPOUND CRYSTAL**(75) Inventors: **Akira Fujishima, Sanda (JP); Isao Aoki, Kawanishi (JP); Keiji Kamiyama, Ibaraki (JP)**(73) Assignee: **Takeda Pharmaceutical Company, Ltd., Osaka (JP)**

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/655,114**(22) Filed: **Sep. 4, 2003**(65) **Prior Publication Data**

US 2004/0048898 A1 Mar. 11, 2004

**Related U.S. Application Data**

(63) Continuation of application No. 10/243,329, filed on Sep. 13, 2002, now Pat. No. 6,664,276, which is a continuation of application No. 09/674,624, filed as application No. PCT/JP00/03881 on Jun. 15, 2000, now Pat. No. 6,462,058.

(30) **Foreign Application Priority Data**

Jun. 17, 1999 (JP) ..... 11-171509

(51) **Int. Cl.<sup>7</sup>** ..... **A61K 31/44; C07D 401/04**(52) **U.S. Cl.** ..... **546/273.7; 514/338**(58) **Field of Search** ..... **546/273.7; 514/338**(56) **References Cited****U.S. PATENT DOCUMENTS**4,628,098 A 12/1986 Nohara et al.  
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*Primary Examiner*—D. Margaret Seaman(74) *Attorney, Agent, or Firm*—Elaine M. Ramesh; Mark Chao(57) **ABSTRACT**

A novel crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof of the present invention is useful for an excellent antiulcer agent.

**17 Claims, No Drawings**

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**BENZIMIDAZOLE COMPOUND CRYSTAL**

This application is a continuation of U.S. patent application Ser. No. 10/243,329 filed on Sep. 13, 2002, now issued U.S. Pat. No. 6,664,276, which was a continuation of U.S. patent application Ser. No. 09/674,624 filed on Nov. 3, 2000, now issued U.S. Pat. No. 6,462,058, which application was the National Stage of International Application No. PCT/JP00/03881, filed on Jun. 15, 2000.

**TECHNICAL FIELD**

The present invention relates to a crystal of a benzimidazole compound showing antiulcer action.

**BACKGROUND ART**

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof having an antiulcer action is reported in JP-A-61-50978, etc.

There is a demand for a more stable and excellently absorbable antiulcer agent.

**DISCLOSURE OF INVENTION**

Having chiral sulfur in the molecular structure thereof, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole occurs in two kinds of optical isomers. After extensive exploration, the present inventors succeeded in optically resolving and crystallizing the (R)-isomer of 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, for the first time found that this crystal serves satisfactorily as a pharmaceutical, made further investigation based on this finding, and developed the present invention.

Accordingly, the present invention relates to:

- [1] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof;
- [2] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole;
- [3] a crystal according to the above [2] wherein the X-ray powder diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom;
- [4] a pharmaceutical composition which comprises the crystal according to the above [1];
- [5] a pharmaceutical composition according to the above [4], which is for treating or preventing digestive ulcer;
- [6] a method for treating or preventing digestive ulcer in a mammal in need thereof which comprises administering to said mammal an effective amount of the crystal according to the above [1] with a pharmaceutically acceptable excipient, carrier or diluent;
- [7] use of the crystal according to the above [1] for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer, and so forth.

The "salt" of "(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof" includes, for example, metal salts, salts with organic bases, salts with basic amino acids, and so forth. Preferred are physiologically acceptable salts.

Metal salts include, for example, alkali metal salts such as sodium salt and potassium salt; and alkaline earth metal salts such as calcium salt, magnesium salt and barium salt. Salts with organic bases include, for example, salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine,

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dicyclohexylamine, N,N-dibenzylethylenediamine, etc. Salts with basic amino acids include, for example, salts with arginine, lysine, etc.

The crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof may be a hydrate or not.

Said "hydrate" includes 0.5 hydrate to 5.0 hydrate. Among others, 0.5 hydrate, 1.0 hydrate, 1.5 hydrate, 2.0 hydrate and 2.5 hydrate are preferred. More preferred is 1.5 hydrate.

The crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof can be produced by subjecting 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof to an optical resolution or subjecting 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole to an asymmetrical oxidation to obtain the (R)-isomer, followed by crystallizing the resultant isomer.

Methods of optical resolution include per se known methods, for example, a fractional recrystallization method, a chiral column method, a diastereomer method, and so forth. Asymmetric oxidation includes per se known methods.

The "fractional recrystallization method" includes a method in which a salt is formed between a racemate and an optically active compound [e.g., (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine, etc.], which salt is separated by fractional recrystallization etc., and, if desired, subjected to a neutralization process, to give a free optical isomer.

The "chiral column method" includes a method in which a racemate or a salt thereof is applied to a column for optical isomer separation (chiral column). In the case of liquid chromatography, for example, optical isomers are separated by adding a racemate to a chiral column such as ENANTIO-OVM (produced by Tosoh Corporation) or the DAICEL CHIRAL series (produced by Daicel Corporation), and developing the racemate in water, a buffer (e.g., phosphate buffer), an organic solvent (e.g., hexane, ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, triethylamine, etc.), or a solvent mixture thereof. In the case of gas chromatography, for example, a chiral column such as CP-Chirasil-DeX CB (produced by GL Science) is used to separate optical isomers.

The "diastereomer method" includes a method in which a racemate and an optically active reagent are reacted (preferably, an optically active reagent is reacted to the 1-position of the benzimidazole group) to give a diastereomer mixture, which is then subjected to ordinary separation means (e.g., fractional recrystallization, chromatography, etc.) to obtain either diastereomer, which is subjected to a chemical reaction (e.g., acid hydrolysis, base hydrolysis, hydrogenolysis, etc.) to cut off the optically active reagent moiety, whereby the desired optical isomer is obtained. Said "optically active reagent" includes, for example, optically active organic acids such as MTPA [ $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic acid] and (-)-menthoxyacetic acid; and optically active alkoxymethyl halides such as (1R-endo)-2-(chloromethoxy)-1,3,3-trimethylbicyclo[2.2.1]heptane, etc.

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof is produced by the methods described in JP-A-61-50978, U.S. Pat. No. 4,628,098 etc. or analogous methods thereto.

Methods of crystallization includes per se known methods, for example, a crystallization from solution, a crystallization from vapor, and a crystallization from molten form.



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Methods of the "crystallization from solution" include, for example, a concentration method, a slow cooling method, a reaction method (diffusion method, electrolysis method), a hydrothermal growth method, a fusing agent method, and so forth. Solvents to be used include, for example, aromatic hydrocarbons (e.g., benzene, toluene, xylene, etc.), halogenated hydrocarbons (e.g., dichloromethane, chloroform, etc.), saturated hydrocarbons (e.g., hexane, heptane, cyclohexane, etc.), ethers (e.g., diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, etc.), nitriles (e.g., acetonitrile, etc.), ketones (e.g., acetone, etc.), sulfoxides (e.g., dimethylsulfoxide, etc.), acid amides (e.g., N,N-dimethylformamide, etc.), esters (e.g., ethyl acetate, etc.), alcohols (e.g., methanol, ethanol, isopropyl alcohol, etc.), water, and so forth. These solvents may be used singly or in mixtures of two or more kinds in appropriate ratios (e.g., 1:1 to 1:100).

Methods of the "crystallization from vapor" include, for example, a gasification method (sealed tube method, gas stream method), a gas phase reaction method, a chemical transportation method, and so forth.

Methods of the "crystallization from molten form" include, for example, a normal freezing method (pulling-up method, temperature gradient method, Bridgman method), a zone melting method (zone leveling method, float zone method), a special growth method (VLS method, liquid phase epitaxis method), and so forth.

For analyzing the crystal obtained, X-ray diffraction crystallographic analysis is commonly used. In addition, crystal orientation can also be determined by a mechanical method, an optical method, etc.

A thus-obtained crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof (hereinafter also referred to as "crystal of the present invention") is useful as a pharmaceutical because it shows excellent antiulcer action, gastric acid secretion-inhibiting action, mucosa-protecting action, anti-*Helicobacter pylori* action, etc., and because it is of low toxicity. Furthermore, by crystallizing the (R)-isomer, not only its stability is improved but also its handling is facilitated so that it can be prepared as a solid pharmaceutical composition with good reproducibility. In addition, when orally administered, the crystal of the present invention is more absorbable and more rapidly shows its action than the racemate. In addition, when administered, the crystal of the present invention shows a higher C<sub>max</sub> (maximum blood concentration) and a greater AUC (area under the concentration-time curve) than the racemate, and becomes less likely to be metabolized partly because of the increased protein-binding rate, thus showing an extended duration of action. The crystal of the present invention is therefore useful as a pharmaceutical of low dosage and with a low prevalence of adverse reactions.

The crystal of the present invention is useful in mammals (e.g., humans, monkeys, sheep, bovines, horses, dogs, cats, rabbits, rats, mice, etc.) for the treatment and prevention of digestive ulcer (e.g., gastric ulcer, duodenal ulcer, stomal ulcer, Zollinger-Ellison syndrome, etc.), gastritis, reflux esophagitis, NUD (non-ulcer dyspepsia), gastric cancer and gastric MALT lymphoma; *Helicobacter pylori* eradication; suppression of upper gastrointestinal hemorrhage due to digestive ulcer, acute stress ulcer and hemorrhagic gastritis; suppression of upper gastrointestinal hemorrhage due to invasive stress (stress from major surgery necessitating intensive management after surgery, and from cerebral vascular disorder, head trauma, multiple organ failure and extensive burns necessitating intensive treatment); treatment

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and prevention of ulcer caused by a nonsteroidal anti-inflammatory agent; treatment and prevention of hyperacidity and ulcer due to postoperative stress; pre-anesthetic administration etc.

The crystal of the present invention is of low toxicity and can be safely administered orally or non-orally (e.g., topical, rectal and intravenous administration, etc.), as such or in the form of pharmaceutical compositions formulated with a pharmacologically acceptable carrier, e.g., tablets (including sugar-coated tablets and film-coated tablets), powders, granules, capsules (including soft capsules), orally disintegrating tablets, liquids, injectable preparations, suppositories, sustained-release preparations and patches, in accordance with a commonly known method.

The content of the crystal of the present invention in the pharmaceutical composition of the present invention is about 0.01 to 100% by weight relative to the entire composition. Varying depending on subject of administration, route of administration, target disease etc., its dose is normally about 0.5 to 1,500 mg/day, preferably about 5 to 150 mg/day, based on the active ingredient, for example, when it is orally administered as an antiulcer agent to an adult human (60 kg). The crystal of the present invention may be administered once daily or in 2 to 3 divided portions per day.

Pharmacologically acceptable carriers that may be used to produce the pharmaceutical composition of the present invention include various organic or inorganic carrier substances in common use as pharmaceutical materials, including excipients, lubricants, binders, disintegrants, water-soluble polymers and basic inorganic salts for solid preparations; and solvents, dissolution aids, suspending agents, isotonicizing agents, buffers and soothing agents for liquid preparations. Other ordinary pharmaceutical additives such as preservatives, antioxidants, coloring agents, sweetening agents, souring agents, bubbling agents and flavorings may also be used as necessary.

Such "excipients" include, for example, lactose, sucrose, D-mannitol, starch, cornstarch, crystalline cellulose, light silicic anhydride and titanium oxide.

Such "lubricants" include, for example, magnesium stearate, sucrose fatty acid esters, polyethylene glycol, talc and stearic acid.

Such "binders" include, for example, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, crystalline cellulose,  $\alpha$ -starch, polyvinylpyrrolidone, gum arabic powder, gelatin, pullulan and low-substitutional hydroxypropyl cellulose.

Such "disintegrants" include (1) crosslinked povidone, (2) what is called super-disintegrants such as crosslinked carmellose sodium (FMC-Asahi Chemical) and carmellose calcium (Gotoku Yakuhin), (3) carboxymethyl starch sodium (e.g., product of Matsutani Chemical), (4) low-substituted hydroxypropyl cellulose (e.g., product of Shin-Etsu Chemical), (5) cornstarch, and so forth. Said "crosslinked povidone" may be any crosslinked polymer having the chemical name 1-ethenyl-2-pyrrolidinone homopolymer, including polyvinylpyrrolidone (PVPP) and 1-vinyl-2-pyrrolidinone homopolymer, and is exemplified by Colidon CL (produced by BASF), Polyplasdon XL (produced by ISP), Polyplasdon XL-10 (produced by ISP) and Polyplasdon INF-10 (produced by ISP).

Such "water-soluble polymers" include, for example, ethanol-soluble water-soluble polymers [e.g., cellulose derivatives such as hydroxypropyl cellulose (hereinafter also referred to as HPC), polyvinylpyrrolidone] and ethanol-insoluble water-soluble polymers [e.g., cellulose derivatives such as hydroxypropylmethyl cellulose (hereinafter also

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referred to as HPMC), methyl cellulose and carboxymethyl cellulose sodium, sodium polyacrylate, polyvinyl alcohol, sodium alginate, guar gum].

Such "basic inorganic salts" include, for example, basic inorganic salts of sodium, potassium, magnesium and/or calcium. Preferred are basic inorganic salts of magnesium and/or calcium. More preferred are basic inorganic salts of magnesium. Such basic inorganic salts of sodium include, for example, sodium carbonate, sodium hydrogen carbonate, disodium hydrogenphosphate, etc. Such basic inorganic salts of potassium include, for example, potassium carbonate, potassium hydrogen carbonate, etc. Such basic inorganic salts of magnesium include, for example, heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite  $[Mg_6Al_2(OH)_{16}CO_3 \cdot 4H_2O]$ , alumina hydroxide magnesium, and so forth. Among others preferred is heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, etc. Such basic inorganic salts of calcium include, for example, precipitated calcium carbonate, calcium hydroxide, etc.

Such "solvents" include, for example, water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil and olive oil.

Such "dissolution aids" include, for example, polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate and sodium citrate.

Such "suspending agents" include, for example, surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and monostearic glycerol; and hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose.

Such "isotonizing agents" include, for example, glucose, D-sorbitol, sodium chloride, glycerol and D-mannitol.

Such "buffers" include, for example, buffer solutions of phosphates, acetates, carbonates, citrates etc.

Such "soothing agents" include, for example, benzyl alcohol.

Such "preservatives" include, for example, p-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid.

Such "antioxidants" include, for example, sulfites, ascorbic acid and  $\alpha$ -tocopherol.

Such "coloring agents" include, for example, food colors such as Food Color Yellow No. 5, Food Color Red No. 2 and Food Color Blue No. 2; and food lake colors and red oxide.

Such "sweetening agents" include, for example, saccharin sodium, dipotassium glycyrrhetinate, aspartame, stevia and thaumatin.

Such "souring agents" include, for example, citric acid (citric anhydride), tartaric acid and malic acid.

Such "bubbling agents" include, for example, sodium bicarbonate.

Such "flavorings" may be synthetic substances or naturally occurring substances, and include, for example, lemon, lime, orange, menthol and strawberry.

The crystal of the present invention may be prepared as a preparation for oral administration in accordance with a commonly known method, by, for example, compression-shaping it in the presence of an excipient, a disintegrant, a binder, a lubricant, or the like, and subsequently coating it as necessary by a commonly known method for the purpose of

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taste masking, enteric dissolution or sustained release. For an enteric preparation, an intermediate layer may be provided by a commonly known method between the enteric layer and the drug-containing layer for the purpose of separation of the two layers.

For preparing the crystal of the present invention as an orally disintegrating tablet, available methods include, for example, a method in which a core containing crystalline cellulose and lactose is coated with the crystal of the present invention and a basic inorganic salt, and is further coated with a coating layer containing a water-soluble polymer, to give a composition, which is coated with an enteric coating layer containing polyethylene glycol, further coated with an enteric coating layer containing triethyl citrate, still further coated with an enteric coating layer containing polyethylene glycol, and still yet further coated with mannitol, to give fine granules, which are mixed with additives and shaped. The above-mentioned "enteric coating layer" includes, for example, aqueous enteric polymer substrates such as cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate, hydroxymethyl cellulose acetate succinate, methacrylic acid copolymers (e.g., Eudragit L30D-55 (trade name); produced by Rohm), Colicoat MAE30DP (trade name); produced by BASF), Polyquid PA30 (trade name; produced by San-yo Chemical)), carboxymethylcellulose and shellac; sustained-release substrates such as methacrylic acid polymers (e.g., Eudragit NE30 D (trade name), Eudragit RL30D (trade name), Eudragit RS30D (trade name), etc.); water-soluble polymers; plasticizers such as triethyl citrate, polyethylene glycol, acetylated monoglycerides, triacetin and castor oil; and mixtures thereof. The above-mentioned "additive" includes, for example, water-soluble sugar alcohols (e.g., sorbitol, mannitol, maltitol, reduced starch saccharides, xylitol, reduced palatinose, erythritol, etc.), crystalline cellulose (e.g., Ceolas KG 801, Avicel PH 101, Avicel PH 102, Avicel PH 301, Avicel PH 302, Avicel RC-591 (crystalline cellulose carmellose sodium)), low-substituted hydroxypropyl cellulose (e.g., LH-22, LH-32, LH-23, LH-33 (Shin-Etsu Chemical) and mixtures thereof); binders, souring agents, bubbling agents, sweetening agents, flavorings, lubricants, coloring agents, stabilizers, excipients, disintegrants etc. are also used.

The crystal of the present invention may be used in combination with 1 to 3 other active ingredients.

Such "other active ingredients" include, for example, anti-*Helicobacter pylori* activity substances, imidazole compounds, bismuth salts, quinolone compounds, and so forth. Of these substances, preferred are anti-*Helicobacter pylori* action substances, imidazole compounds etc. Such "anti-*Helicobacter pylori* action substances" include, for example, antibiotic penicillins (e.g., amoxicillin, benzylpenicillin, piperacillin, mecillinam, etc.), antibiotic cefems (e.g., cefixime, cefaclor, etc.), antibiotic macrolides (e.g., erythromycin, clarithromycin, etc.), antibiotic tetracyclines (e.g., tetracycline, minocycline, streptomycin, etc.), antibiotic aminoglycosides (e.g., gentamicin, amikacin, etc.), imipenem and so forth. Of these substances, preferred are antibiotic penicillins, antibiotic macrolides etc. Such "imidazole compounds" include, for example, metronidazole, miconazole, etc. Such "bismuth salts" include, for example, bismuth acetate, bismuth citrate, etc. Such "quinolone compounds" include, for example, ofloxacin, ciprofloxacin, etc.

Such "other active ingredients" and the crystal of the present invention may also be used in combination as a mixture prepared as a single pharmaceutical composition

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[e.g., tablets, powders, granules, capsules (including soft capsules), liquids, injectable preparations, suppositories, sustained-release preparations, etc.], in accordance with a commonly known method, and may also be prepared as separate preparations and administered to the same subject simultaneously or at a time interval.

#### BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is hereinafter described in more detail by means of, but is not limited to, the following reference examples and experimental examples.

In the following reference examples and examples, the term "room temperature" indicates about 15 to 30° C.

Melting points were measured using the Micro Melting Point Apparatus (produced by Yanagimoto Seisakusho), and uncorrected values are shown.

<sup>1</sup>H-NMR spectra were determined with CDCl<sub>3</sub> as the solvent using Varian Gemini-200; data are shown in chemical shift  $\delta$  (ppm) from the internal standard tetramethylsilane.

IR was determined using SHIMADZU FTIR-8200.

UV was determined using the HITACHI U-3200 spectrophotometer.

Optical rotation  $[\alpha]_D$  was determined at 20° C. using the DIP-370 digital polarimeter (produced by JASCO).

Optical purity was determined by HPLC (column: CHIRALCEL OD 4.6 mm dia. x 250 mm, temperature: about 20° C., mobile phase: hexane/2-propanol=80/20 or hexane/2-propanol=85/15, flow rate: 1.0 ml/min, detection wavelength: 285 nm) using a chiral column.

Crystal X-ray diffraction data for determining the absolute structure of sulfoxide were obtained by means of a 4-circle diffractometer (RIGAKU AFC5R) using the Cu-K $\alpha$  ray. After the initial phase was determined by the direct method, the fine structure was analyzed using SHELXL-93. X-ray powder diffraction was determined using the X-ray Powder Diffraction meter Rigaku RINT2500 (ultraX18) No. PX-3.

The other symbols used herein have the following definitions:

- s: singlet
- d: doublet
- t: triplet
- q: quartet
- m: multiplet
- bs: broad singlet
- J: binding constant

#### EXAMPLES

##### Reference Example 1

Isolation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (lansoprazole) (racemate) (3.98 g) was dissolved in the following mobile phase (330 ml) and acetonitrile (37 ml) and fractionated by HPLC (column: CHIRALCEL OD 20 mm dia. x 250 mm, temperature: 30° C., mobile phase: hexane/2-propanol/ethanol=255/35/10, flowrate: 16 ml/min, detection wavelength: 285 nm, 1 shot: 20–25 mg). Fractions of optical

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isomers of shorter retention time were combined and concentrated; the individual lots were combined and dissolved in ethanol and filtered through a 0.45  $\mu$ m filter; after hexane was added, the filtrate was again evaporated to dryness to yield R(+)-lansoprazole (1.6 g, optical purity>97.6% ee) as an amorphous substance.

The amorphous substance obtained was subjected to fractionation and isolation in the same manner as above to yield R(+)-lansoprazole (1.37 g, optical purity>99.9% ee) as an amorphous substance.

$[\alpha]_D^{20}=+174.3^\circ$  (c=0.994%, CHCl<sub>3</sub>)

##### Reference Example 2

Isolation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

Lansoprazole (racemate) (34.2 g) was dissolved in 2-propanol (1,710 ml) and hexane (1,140 ml) containing triethylamine (0.2%) and fractionated by HPLC (column: CHIRALCEL OD 50 mm dia. x 500 mm, temperature: room temperature, mobile phase: hexane/2-propanol=85/15, flow rate: 60 ml/min, detection wavelength: 285 nm, single injection: about 300 mg) to isolate the individual optical isomers. Fractions of an optical isomer of shorter retention time were combined and concentrated; the individual lots were combined and dissolved in ethanol (250 ml); after triethylamine (3 ml) was added, the solution was filtered through a 0.45  $\mu$ m filter. After the filtrate was concentrated, hexane was added, and the filtrate was again evaporated to dryness to yield R(+)-lansoprazole (9.31 g, optical purity 98.3% ee) as an amorphous substance.

##### Reference Example 3

Production of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

In a nitrogen atmosphere, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]benzimidazole (20.0 g, 0.057 mol), toluene (100 ml), water (55 mg, 0.0031 mol as based on total water content) and diethyl (+)-tartrate (2.12 ml, 0.012 mol) were mixed and stirred at 50 to 55° C. for 30 minutes. After titanium (IV) isopropoxide (1.66 ml, 0.0057 mol) was added to the mixture in a nitrogen atmosphere, the mixture was stirred at 50 to 55° C. for 1 hour. After diisopropylethylamine (3.25 ml, 0.019 mol) was added to the resulting mixed liquor under cooling in a nitrogen atmosphere, cumene hydroperoxide (30.6 ml, content 82%, 0.17 mol) was added at 0 to 5° C., followed by 3.5 hours of stirring at 0 to 5° C., to cause the reaction.

Analysis of the reaction liquor by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfide at 1.32% and a sulfone at 1.81% as related substances in the reaction liquor, with no other related substances detected. The enantiomer excess rate of the title compound in said reaction liquor was 96.4% ee.

##### Reference Example 4

Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

(1) In a nitrogen stream, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio]benzimidazole (4.5



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kg, 12.7 mol, containing 1.89 g of water), toluene (22 l), water (25 g, 1.39 mol, or 1.49 mol if based on total water content) and diethyl (+)-tartrate (0.958 l, 5.60 mol) were mixed. In a nitrogen stream, titanium (IV) isopropoxide (0.747 l, 2.53 mol) was added to this mixture at 50 to 60° C., and the mixture was stirred at the above temperature for 30 minutes. After diisopropylethylamine (0.733 l, 4.44 mol) was added to the resulting mixed liquor at room temperature in a nitrogen stream, cumene hydroperoxide (6.88 l, content 82%, 37.5 mol) was added at -5 to 5° C., followed by 1.5 hours of stirring at -5 to 5° C., to yield a reaction liquor.

Analysis of the reaction liquor by HPLC (column: Capcell Pak (Shiseido, Co. Ltd.), mobile phase: solvent mixture (acetonitrile/water/triethylamine=50/50/1); adjusted to pH 7.0 with phosphoric acid, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfide at 1.87% and a sulfone at 1.59% as related substances in the reaction liquor, with no other related substances detected.

(2) To the reaction liquor obtained in (1 l) above, a 30% aqueous solution of sodium thiosulfate (17 l) was added, in a nitrogen stream, to decompose the residual cumene hydroperoxide. To the organic layer obtained by liquid separation, water (4.5 l), heptane (13.5 l), t-butyl methyl ether (18 l) and heptane (27 l) were added sequentially in this order, and this mixture was stirred to cause crystallization. The resulting crystal was separated and washed with t-butyl methyl ether-toluene (t-butyl methyl ether:toluene=4:1) (4 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 5.85, 4.70, 4.35, 3.66 and 3.48 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfone at 0.90% as a related substance in the crystal, with no sulfide or any other related substance detected. The (R)-lansoprazole enantiomer excess rate in this crystal was 100% ee.

(3) With stirring, a suspension in acetone (20 l) of the wet crystal obtained in (2) above was added drop by drop into a mixed liquor of acetone (7 l) and water (34 l), then water (47 l) was added; The precipitated crystal was separated and washed with acetone-water (acetone:water=1:3) (4 l) and water (12 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100% ee.

(4) After the wet crystal obtained in (3) above was dissolved in ethyl acetate (45 l) and water (3 l), this solution was divided into liquid layers. The trace amount of insoluble

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matter in the organic layer was filtered off, then triethylamine (0.2 l) was added, after which the filtrate was concentrated under reduced pressure to a liquid volume of about 7 l. To this concentrate, methanol (2.3 l), about 12.5% aqueous ammonia at about 50° C. (23 l) and t-butyl methyl ether at about 50° C. (22 l) were added, and this liquid was divided into layers. To the organic layer, about 12.5% aqueous ammonia (11 l) was added, and this liquid was divided into layers (this operation was repeated once again). The water layers were combined, and ethyl acetate (22 l) was added, and then acetic acid was added drop by drop to reach a pH of about 8 under cooling. The liquid was divided into layers, and the water layer was extracted with ethyl acetate (11 l). The organic layers were combined and washed with about 20% saline (11 l). After triethylamine (0.2 l) was added, the organic layer was concentrated under reduced pressure. Acetone (5 l) was added to the concentrate, and this mixture was concentrated under reduced pressure. The concentrate was dissolved in acetone (9 l), and this solution was added drop by drop into a mixed liquor of acetone (4.5 l) and water (22.5 l), and then water (18 l) was added drop by drop to the mixed liquor obtained. The precipitated crystal was separated and washed sequentially with cold acetone-water (acetone:water=1:3) (3 l) and water (12 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100% ee.

(5) The wet crystal obtained in (4) above was dissolved in ethyl acetate (32 l). The water layer was separated by a liquid separation procedure, and the organic layer obtained was concentrated under reduced pressure to a liquid volume of about 14 l. To the residual liquid, ethyl acetate (36 l) and activated charcoal (270 g) were added, after stirring, the activated charcoal was removed by filtration. The filtrate was concentrated under reduced pressure to a liquid volume of about 14 l. At about 40° C., heptane (90 l) was added drop by drop to the residual liquid. After stirring at the above temperature for about 30 minutes, the resulting crystal was separated, washed with about 40° C. ethyl acetate-heptane (ethyl acetate:heptane=1:8) (6 l), and dried to yield 3.4 kg of the title compound.

The results of powder X-ray diffraction analysis of this crystal are shown below.

The crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100% ee.

#### Example 1

Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

Amorphous R(+)-lansoprazole as obtained in Reference Example 1 (100 mg) was dissolved in acetonitrile (1 ml),

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which was gradually evaporated at room temperature in a nitrogen stream. After a crystal began to form, diethyl ether (1.5 ml) was added and the container was stoppered and kept standing at room temperature.

The crystal thus formed was subjected to X-ray structural analysis, and the absolute configuration of sulfoxide was found to be the R-configuration by a method using a Flack parameter. The remaining portion of the crystal was collected by filtration, twice washed with diethyl ether (1 ml), and dried under reduced pressure, to yield crystals of R(+)-lansoprazole (38 mg).

m.p.: 144.0–144.5° C. (dec.) Elemental analysis Calculated: C: 52.03, H: 3.82, N: 11.38, S: 8.68, F: 15.43, O: 8.66 Found: C: 52.08, H: 3.76, N: 11.58, S: 8.75, F: 15.42 <sup>1</sup>H-NMR: 2.25(3H, s), 4.40(2H, q, J=7.8 Hz), 4.68(1H, d, J=13.8 Hz), 4.85(1H, d, J=13.8 Hz), 6.69(1H, d, J=6.0 Hz), 7.29–7.39(2H, m), 7.52(1H, m), 7.81(1H, m), 8.37(1H, d, J=6.0 Hz), 11.00(1H, bs).

IR(vcm<sup>-1</sup>): 3081, 3042, 2984, 1586, 1478, 1441, 1306, 1267, 1163. UVmax(CHCl<sub>3</sub>): 283.7 nm [ $\alpha$ ]<sub>D</sub>=+199.2° (c=0.202%, CHCl<sub>3</sub>)

TABLE 1

Crystal Data and Structure Refinement Parameters	
Molecular formula	C <sub>16</sub> H <sub>14</sub> N <sub>3</sub> O <sub>2</sub> F <sub>3</sub> S
Molecular weight	369.36
Crystal color, habit	Colorless, tabular
Crystal Dimension	0.40 × 0.30 × 0.04 (mm)
Crystal system	Monoclinic
Lattice constants	a = 8.549(1) (Å) b = 23.350(1) (Å) c = 8.720(2) (Å) β = 103.90(1) (°) V = 1,689.8(4) (Å <sup>3</sup> )
Space group	P2 <sub>1</sub>
Z	4
Density (calculated)	1.452 (g/cm <sup>3</sup> )
Effective reflection number/parameter number	9.12
R (I = 2σ(I))	0.036
Flack parameter	−0.02(2)

## Example 2

Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole)

Amorphous (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole as obtained in Reference Example 2 (9.17 g) was dissolved in acetone (20 ml), and water (15 ml) was added with gentle heating. After the solution was kept standing at room temperature overnight, water (20 ml) was added, followed by ultrasonication. After being collected by filtration, the solid was washed with water (30 ml, 20 ml), then washed with diisopropyl ether (20 ml), and dried under reduced pressure, to yield a solid (9.10 g). The solid obtained (9.00 g) was dissolved in acetone (30 ml), and after the solution was filtered, diisopropyl ether (50 ml) was added to the filtrate. A crystal seed was placed, and the mixture was kept standing at room temperature overnight. Precipitated crystals were collected by filtration, washed 3 times with diisopropyl ether (10 ml), and dried under reduced pressure, to yield crystals (7.85 g). The crystals obtained (7.80 g) were dissolved under heating in acetone (22.5 ml) and water (30 ml), and this solution was kept standing at room temperature for 1 hour. A precipitated solid was collected by filtration, washed with

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acetone-water (1:4) (15 ml), and dried under reduced pressure, to yield a solid (3.88 g). The solid obtained (3.88 g) was dissolved under heating in acetone (4 ml) and diisopropyl ether (14 ml) was added. This solution was kept standing at room temperature for 30 minutes. Precipitated crystals were collected by filtration, twice washed with diisopropyl ether (6 ml), and dried under reduced pressure, to yield crystals of R(+)-lansoprazole (3.40 g, optical purity 99.8% ee).

m.p.: 147.0–148.0° C. (dec.) Elemental analysis Calculated: C: 52.03, H: 3.82, N: 11.38, S: 8.68, F: 15.43, O: 8.66 Found: C: 51.85, H: 3.92, N: 11.26, S: 8.82, F: 15.22 <sup>1</sup>H-NMR: 2.24(3H, s), 4.38(2H, q, J=7.8 Hz), 4.74(1H, d, J=13.6 Hz), 4.87(1H, d, J=13.6 Hz), 6.68(1H, d, J=5.8 Hz), 7.26–7.36(2H, m), 7.45(1H, m), 7.78(1H, m), 8.35(1H, d, J=5.8 Hz). IR(vcm<sup>-1</sup>): 3083, 3034, 2975, 1586, 1478, 1441, 1306, 1267, 1163 UVmax (CHCl<sub>3</sub>): 283.6 nm [ $\alpha$ ]<sub>D</sub>=+180.3° (c=1.004%, CHCl<sub>3</sub>)

TABLE 2

X-ray Powder Diffraction Data			
2θ (°)	Half-value width	d-value (Å)	Relative intensity (%)
7.560	0.141	11.6841	100
13.060	0.165	6.7733	44
15.160	0.141	5.8394	55
15.440	0.141	5.7342	84
20.040	0.165	4.4271	23
21.720	0.165	4.0883	89
22.560	0.141	3.9380	24
22.820	0.141	3.8937	24
24.080	0.165	3.6927	37
26.120	0.118	3.4088	32
28.680	0.165	3.1100	20

## Example 3

Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) 1.5 hydrate

Amorphous (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole as obtained in Reference Example 1 (100 mg) was dissolved in ethanol (0.15 ml), and water (0.15 ml) was added. After a seed was placed, the solution was kept standing at room temperature for 1 hour. Precipitated crystals were collected by filtration, twice washed with water (2 ml), and dried under reduced pressure, to yield crystals of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) 1.5 hydrate (96 mg).

m.p.: 76.0–80.0° C. Elemental analysis Calculated: C: 48.48, H: 4.32, N: 10.60, S: 8.09, F: 14.38, O: 14.13 Found: C: 48.52, H: 4.44, N: 10.49

TABLE 3

X-ray Powder Diffraction Data			
2θ (°)	Half-value width	d-value (Å)	Relative intensity (%)
6.680	0.165	13.2212	9
9.200	0.165	9.6046	21
9.960	0.141	8.8734	25
10.980	0.165	8.0513	42
13.380	0.141	6.6120	22

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TABLE 3-continued

X-ray Powder Diffraction Data			
2 $\theta$ (°)	Half-value width	d-value (Å)	Relative intensity (%)
14.960	0.141	5.9170	63
15.680	0.165	5.6469	100
17.640	0.212	5.0237	34
19.760	0.212	4.4892	33
25.420	0.188	3.5010	23
29.800	0.188	2.9957	20

## Experimental Example 1

Suppressive action on gastric mucosal injury due to stress of water immersion restraint in rat

Male SD rats (7 weeks of age, weighing 230 to 250 g) were fasted for 24 hours, after which they were stressed by being housed in restraint cages and immersed to below the xiphoid process in a standing position in a 23° C. constant-temperature water chamber. After 5 hours, the rats were removed from the cages and sacrificed using gaseous carbon dioxide, and their stomachs excised. After the lower portion of the esophagus was clipped, a 1% formalin solution (10 ml) was injected into the stomach via the duodenum, which was then occluded, and the stomach was immersed in the same solution. After 10 minutes, an incision was made along the greater curvature, and the length (mm) of each mucosal injury was measured under a stereomicroscope. The overall sum of the injury lengths in each stomach was taken as the gastric mucosal injury index.

The crystals of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) as obtained in Example 2 were suspended in 0.5% methyl cellulose (pH 9.5) containing 0.05 M NaHCO<sub>3</sub> and orally administered at 30 minutes before stressing (dosing volume 2 ml/kg). Each treatment group comprised 9 animals. The control group (solvent administration group) and the drug administration group were compared by Steel's test.

The results are shown in Table 4.

TABLE 4

Sample	Dose (mg/kg)	Gastric mucosal injury index (mm)	Suppression rate (%)
Control	—	10.9 ± 1.9	—
(R)-lansoprazole crystal	3	0.2 ± 0.2*	98.0

Each figure of gastric mucosal injury index is the mean ± standard error for the 9 animals in each group. \*p < 0.01 (versus control group, Steel's test)

## Experimental Example 2

The crystals of R(+)-lansoprazole as obtained in Example 2 (about 5 mg) and amorphous R(+)-lansoprazole as obtained in Reference Example 1 (about 5 mg) were each taken in a colorless glass bottle, and their stability during storage at 60° C. (stopper removed) was examined. A 25 ml solution (concentration: about 0.2 mg/ml) of the sample after completion of storage in the mobile phase, along with a standard solution prepared using the initial lot, was analyzed under the HPLC conditions shown below, and the R(+)-lansoprazole content (residual percentage) was calculated from the peak area obtained. The results are shown in Table 5.

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HPLC analytical conditions

5	Detection wavelength	UV 275 nm
	Column	YMC Pro C18, 4.6 × 150 mm
	Mobile phase	Fluid prepared by adding phosphoric acid to water/acetonitrile/triethylamine (63:37:1) to reach pH 7.
10	Flow rate	1.0 ml/min
	Column temperature	40° C.
	Sample injection volume	10 $\mu$ l

TABLE 5

Stability of R(+)-Lansoprazole Crystal and Amorphous

Sample	Duration of storage	Description	Content (Residual percentage)
20	Crystal	1 week	Light-brown 97.0
		2 weeks	Brown 93.8
		4 weeks	Brown 91.7
	Amorphous	1 week	Brown 70.8
		2 weeks	Blackish brown 57.5

When the sample was stored at 60° C. (exposed), the crystal of Example 2 retained a content exceeding 90% for up to 4 weeks, whereas the amorphous form of Reference Example 1 showed reduction in content to 70.8% after 1 week and 57.5% after 2 weeks. This finding demonstrates that the crystal of R(+)-lansoprazole is more stable and more preferable for use as a pharmaceutical etc. than the amorphous form.

## INDUSTRIAL APPLICABILITY

The crystal of the present invention is useful as a pharmaceutical because it shows excellent antiulcer action, gastric acid secretion-inhibiting action, mucosa-protecting action, anti-*Helicobacter pylori* action etc., and because it is of low toxicity. Furthermore, by crystallizing the (R)-isomer, not only its stability is improved but also its handling is facilitated so that it can be prepared as a solid pharmaceutical composition with good reproducibility. In addition, when orally administered, the crystal of the present invention is more absorbable and more rapidly shows its action than the racemate. In addition, when administered, the crystal of the present invention shows a higher C<sub>max</sub> and a greater AUC than the racemate, and becomes less likely to be metabolized partly because of the increased protein-binding rate, thus showing an extended duration of action. The crystal of the present invention is therefore useful as a pharmaceutical of low dosage and with a low prevalence of adverse reactions.

What is claimed is:

1. A method of treating Zollinger-Ellison syndrome in a mammal in need thereof which comprises administering to said mammal an effective amount of a crystalline compound of (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole or a salt thereof and a pharmaceutically acceptable excipient, carrier or diluent.

2. The method of claim 1 wherein said crystalline compound is (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole.

3. The method of claim 2 wherein said crystalline compound has an X-ray powder diffraction analysis pattern with characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

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4. The method of claim 1 wherein said crystalline compound is (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole 1.5 hydrate and has an X-ray powder diffraction analysis pattern with characteristic peaks at interplanar spacings (d) of 13.22, 9.60, 8.87, 8.05, 6.61, 5.92, 5.65, 5.02, 4.49, 3.50 and 3.00 Angstrom.

5. A method of treating reflux esophagitis in a mammal in need thereof which comprises administering to said mammal an effective amount of a crystalline compound of (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole or a salt thereof and a pharmaceutically acceptable excipient, carrier or diluent.

6. The method of claim 5 wherein said crystalline compound is (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole.

7. The method of claim 6 wherein said crystalline compound has an X-ray powder diffraction analysis pattern with characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

8. The method of claim 5 wherein said crystalline compound is (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole 1.5 hydrate and has an X-ray powder diffraction analysis pattern with characteristic peaks at interplanar spacings (d) of 13.22, 9.60, 8.87, 8.05, 6.61, 5.92, 5.65, 5.02, 4.49, 3.50 and 3.00 Angstrom.

9. A method of eradicating *Helicobacter pylori* in a mammal in need thereof which comprises administering to said mammal an effective amount of a crystalline compound of (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole or a salt thereof and a pharmaceutically acceptable excipient, carrier or diluent.

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10. The method of claim 9 further comprising administering one to three other active ingredients.

11. The method of claim 10 wherein said crystalline compound and said other active ingredient are administered simultaneously or in intervals.

12. The method of claim 10 wherein said other active ingredient is selected from the group consisting of an anti-*Helicobacter pylori* action substance, an imidazole compound, a bismuth salt, a quinoline compound and combinations thereof.

13. The method of claim 12 wherein said anti-*Helicobacter pylori* action substance is selected from the group consisting of antibiotic penicillins, antibiotic macrolides and combinations thereof.

14. The method of claim 12 wherein said imidazole compound is metronidazole.

15. The method of claim 9 wherein said crystalline compound is (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole.

16. The method of claim 15 wherein said crystalline compound has an X-ray powder diffraction analysis pattern with characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

17. The method of claim 9 wherein said crystalline compound is (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole 1.5 hydrate and has an X-ray powder diffraction analysis pattern with characteristic peaks at interplanar spacings (d) of 13.22, 9.60, 8.87, 8.05, 6.61, 5.92, 5.65, 5.02, 4.49, 3.50 and 3.00 Angstrom.

\* \* \* \* \*

# **EXHIBIT D**



(12) **United States Patent**  
**Hashimoto et al.**

(10) **Patent No.:** **US 7,285,668 B2**  
(45) **Date of Patent:** **\*Oct. 23, 2007**

(54) **PROCESS FOR THE CRYSTALLIZATION OF (R)- OR (S)-LANSOPRAZOLE**

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(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(57) **ABSTRACT**

The present invention relates to a production method of a crystal of (R)-lansoprazole or (S)-lansoprazole, which includes crystallization at a temperature of about 0° C. to about 35° C. from a C<sub>1-4</sub> alkyl acetate solution containing (R)-lansoprazole or (S)-lansoprazole at a concentration of about 0.1 g/mL to about 0.5 g/mL and the like. According to the production method of the present invention, a crystal of (R)-lansoprazole or (S)-lansoprazole superior in preservation stability can be produced efficiently on an industrial large scale.

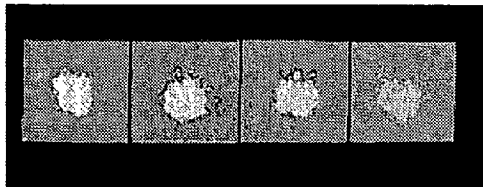
**13 Claims, 1 Drawing Sheet**

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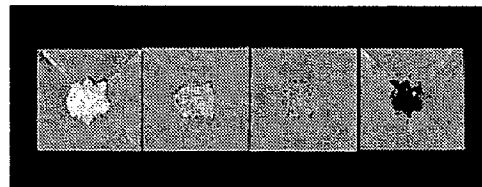
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**FIG. 1**



Initial    40°C    50°C    60°C  
          2W        2W        2W

Method of present invention  
(melting start temperature:  
about 134°C)



Initial    40°C    50°C    60°C  
          2W        2W        2W

Conventional method  
(melting start temperature:  
about 130°C)

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**PROCESS FOR THE CRYSTALLIZATION OF  
(R)- OR (S)-LANSOPRAZOLE**

This application is the National Phase filing of International Patent Application No. PCT/JP01/10462, filed 30 Nov. 2001.

**TECHNICAL FIELD**

The present invention relates to production methods of an optically active sulfoxide compound having an antiulcer activity, a crystal of an optically active sulfoxide compound having remarkably improved stability, and the like.

**BACKGROUND ART**

As a method for producing (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole [hereinafter sometimes to be referred to as (R)-lansoprazole] or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole [hereinafter sometimes to be referred to as (S)-lansoprazole] having an antiulcer activity, for example, JP-A-11-508590 (WO 97/02261) describes a method for optically purifying a compound product adjusted to contain an enriched enantiomer and crystallization method by removing the solvent, which comprises treating a compound containing either (+)-enantiomer or (−)-enantiomer in a greater amount, namely, a compound enriched in one enantiomer, with a solvent, selectively precipitating a racemic compound from the solvent utilizing the crystallinity of the racemate, filtering off the precipitated racemic compound and removing the solvent to give a single enantiomer of the compound having an increased optical purity, which corresponds to lansoprazole and the like.

JP-A-10-504290 (WO 96/02535) describes a production method of an optically active sulfoxide compound, which comprises subjecting a thio compound to an oxidation reaction, and crystallization (Example 11) of omeprazole, which comprises concentrating an acetonitrile solution and the like.

Lansoprazole is now on the market worldwide as a pharmaceutical product having a superior antiulcer activity. The crystal of lansoprazole is a racemate and is superior in preservation stability.

A crystal of optically active (R)-lansoprazole and (S)-lansoprazole obtained according to the above-mentioned conventional method does not necessarily satisfy the preservation stability, with the undeniable possibility of decreased purity, increased amounts of analogous materials, coloring and the like during preservation.

Therefore, there is a demand for a production method of the crystal of (R)-lansoprazole or (S)-lansoprazole sufficiently superior in the preservation stability.

**DISCLOSURE OF INVENTION**

As a result of various studies of the production methods of crystals of (R)-lansoprazole and (S)-lansoprazole, the present inventors have unexpectedly found for the first time that crystallization of (R)-lansoprazole and (S)-lansoprazole under specific conditions produces an extremely stable crystal and that this method is sufficiently satisfactory on an industrial scale, and completed the present invention.

Accordingly, the present invention provides the following:

[1] a method for producing a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-

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benzimidazole, which comprises crystallizing at a temperature of about 0° C. to about 35° C. from a C<sub>1-4</sub> alkyl acetate solution containing (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole at a concentration of about 0.1 g/mL to about 0.5 g/mL;

[2] a method for producing a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, which comprises crystallizing at a temperature of about 0° C. to about 35° C. from a C<sub>1-4</sub> alkyl acetate solution containing (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole at a concentration of about 0.1 g/mL to about 0.5 g/mL, and adding dropwise to the C<sub>1-4</sub> alkyl acetate solution, at the same temperature, C<sub>5-8</sub> hydrocarbon in an amount of not more than 7 times the amount of the C<sub>1-4</sub> alkyl acetate solution;

[3] the method of the above-mentioned [1] or [2], wherein the crystallization temperature is about 20° C. to about 30° C.;

[4] the method of the above-mentioned [1] or [2] wherein the crystallization is conducted for about 30 minutes to about 4 hours;

[5] the method of the above-mentioned [1] or [2], wherein the C<sub>1-4</sub> alkyl acetate is ethyl acetate or propyl acetate;

[6] the method of the above-mentioned [2], wherein the C<sub>5-8</sub> hydrocarbon is added in an amount of not more than 5 times the amount of the C<sub>1-4</sub> alkyl acetate solution;

[7] the method of the above-mentioned [2], wherein the C<sub>5-8</sub> hydrocarbon is heptane or hexane;

[8] the method of the above-mentioned [2], wherein the C<sub>5-8</sub> hydrocarbon is added dropwise over about 15 minutes to about 4 hours;

[9] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole produced according to the method of the above-mentioned [1] or [2];

[10] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole produced according to the method of the above-mentioned [1] or [2];

[11] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole having a melting start temperature of not lower than about 131° C.;

[12] the crystal of the above-mentioned [11], wherein the melting start temperature is about 135° C.;

[13] a pharmaceutical composition containing the crystal of the above-mentioned [9] or [11];

[14] the pharmaceutical composition of the above-mentioned [13], which is for the prophylaxis or treatment of digestive ulcer, gastritis, reflux esophagitis, NUD (Non Ulcer Dyspepsia), gastric cancer, gastric MALT lymphoma, upper gastrointestinal hemorrhage, ulcer caused by a nonsteroidal anti-inflammatory agent, hyperacidity and ulcer due to postoperative stress, or a disease due to *Helicobacter pylori*;

[15] a method of preventing or treating digestive ulcer, gastritis, reflux esophagitis, NUD (Non Ulcer Dyspepsia), gastric cancer, gastric MALT lymphoma, upper gas-

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trointestinal hemorrhage, ulcer caused by a nonsteroidal anti-inflammatory agent, hyperacidity and ulcer due to postoperative stress, or a disease due to *Helicobacter pylori*, which comprises administering the crystal of the above-mentioned [9] or [11] to human;

[16] use of the crystal of the above-mentioned [9] or [11] for the production of a pharmaceutical composition for the prophylaxis or treatment of digestive ulcer, gastritis, reflux esophagitis, NUD (Non Ulcer Dyspepsia), gastric cancer, gastric MALT lymphoma, upper gastrointestinal hemorrhage, ulcer caused by a nonsteroidal anti-inflammatory agent, hyperacidity and ulcer due to postoperative stress, or a disease due to *Helicobacter pylori*;

[17] a method for stabilizing a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, which comprises crystallizing at a temperature of about 0° C. to about 35° C. from a C<sub>1-4</sub> alkyl acetate solution containing (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole at a concentration of about 0.1 g/mL to about 0.5 g/mL; and the like.

#### BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 shows the appearance of a crystal (Example 1) having a melting start temperature of about 134° C. and a crystal (Reference Example 6) having a melting start temperature of about 130° C., before stability test (initial) and after stability test at 40° C. for 2 weeks, 50° C. for 2 weeks and 60° C. for 2 weeks.

#### DETAILED DESCRIPTION OF THE INVENTION

The "(R)-lansoprazole" or "(S)-lansoprazole" used as a starting material in the crystal production method of the present invention can be produced according to a method known per se, such as the method described in JP-A-10-504290 (WO 96/02535) or a method analogous thereto, or the method described in the following production method 1 or 2.

##### (1) Production Method 1

2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole and an excess amount (about 1.5-10 molar equivalents) of an oxidant (e.g., peroxide such as hydrogen peroxide, tert-butyl hydroperoxide, cumene hydroperoxide, etc.) are reacted in the presence of a catalyst for asymmetric induction (e.g., optically active diol, complex of titanium(IV) alkoxide and water, etc.), an organic solvent [e.g., alcohols such as methanol, ethanol, propanol, isopropanol etc.; aromatic hydrocarbons such as benzene, toluene, xylene etc.; ethers such as diethyl ether, diisopropyl ether, butyl methyl ether, dioxane, tetrahydrofuran etc.; esters such as ethyl acetate, methyl acetate etc.; ketones such as acetone, methyl isobutyl ketone etc.; halogenated hydrocarbons such as chloroform, dichloromethane, ethylene dichloride, carbon tetrachloride etc.; amides such as N,N-dimethylformamide etc.; sulfoxides such as dimethylsulfoxide etc.; acetic acid and the like] and a base [such as an inorganic base (e.g., alkali metal carbonates (potassium carbonate, sodium carbonate etc.), alkali metal hydroxides (sodium hydroxide, potassium hydroxide etc.), alkali metal hydrides (sodium hydride, potassium hydride etc.) etc.); an organic base such as alkali metal alkoxides (sodium meth-

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oxide, sodium ethoxide, etc.), alkali metal carboxylates (sodium acetate, etc.), amines (piperidine, piperazine, pyrrolidine, morpholine, triethylamine, tripropylamine, tributylamine, trioctylamine, diisopropylethylamine, dimethylphenylamine, etc.), pyridines (pyridine, dimethylaminopyridine, etc.) and the like; a basic amino acid (e.g., arginine, lysin, ornithine etc.) and the like], at about -20° C. to 20° C. for about 0.1 to 50 hours.

The obtained compound can be isolated by a separation and purification method known per se, such as concentration, solvent extraction, crystallization, redissolution, chromatography or a combination thereof.

##### (2) Production Method 2

2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole is subjected to optical resolution to give an isomer.

The method of optical resolution includes a method known per se, for example, a fractional recrystallization method, a chiral column method, a diastereomer method, and so forth.

The "fractional recrystallization method" includes a method in which a salt is formed between a racemate and an optically active compound [e.g., (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine, etc.], which salt is separated by fractional recrystallization etc., and, if desired, subjected to a neutralization process, to give a free optical isomer.

The "chiral column method" includes a method in which a racemate or a salt thereof is applied to a column for separation of optical isomer (chiral column). In the case of liquid chromatography, for example, optical isomers are separated by adding a racemate to a chiral column such as ENANTIO-OVM (produced by Tosoh Corporation) or the DAICEL CHIRAL series (produced by Daicel Corporation), and developing the racemate in water, a buffer (e.g., phosphate buffer), an organic solvent (e.g., hexane, ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, triethylamine, etc.), or a solvent mixture thereof. In the case of gas chromatography, for example, a chiral column, such as CP-Chirasil-DeX CB (produced by GL Science), is used to separate optical isomers.

The "diastereomer method" includes a method in which a racemate and an optically active reagent are reacted (preferably, an optically active reagent is reacted with the 1-position of the benzimidazole group) to give a diastereomer mixture, which is then subjected to ordinary separation methods (e.g., fractional recrystallization, chromatography, etc.) to obtain either diastereomer, which is subjected to a chemical reaction (e.g., acid hydrolysis, base hydrolysis, hydrogenolysis, etc.) to cut off the optically active reagent moiety, whereby the desired optical isomer is obtained. Said "optically active reagent" includes, for example, optically active organic acids such as MTPA [ $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic acid] and (-)-menthoxyacetic acid; and optically active alkoxymethyl halides such as (1R-endo)-2-(chloromethoxy)-1,3,3-trimethylbicyclo[2.2.1]heptane and the like.

The above-mentioned 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole can be produced according to the method described in JP-A-61-50978, U.S. Pat. No. 4,628,098, JP-A-10-195068, WO 98/21201 and the like or a method analogous thereto.

2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole is produced by the method described in JP-A-61-50978, U.S. Pat. No. 4,628,098 etc. or a method analogous thereto.



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The (R)-lansoprazole or (S)-lansoprazole produced by the above-mentioned method may be a solid (crystal, amorphous) or an oily substance and may not be isolated or purified.

The crystal of (R)-lansoprazole or (S)-lansoprazole may or may not be a hydrate.

The "hydrate" includes 0.5 hydrate to 5.0 hydrate. Among others, 0.5 hydrate, 1.0 hydrate, 1.5 hydrate, 2.0 hydrate and 2.5 hydrate are preferred. More preferred is 0.5 hydrate, 1.0 hydrate and 1.5 hydrate.

When the (R)-lansoprazole or (S)-lansoprazole obtained according to the above-mentioned method as, for example, a crystal (hereinafter sometimes to be referred to as crystal (I)) and then subjected to the crystal production method of the present invention, the method of crystallization of crystal (I) includes methods known per se, for example, crystallization from a solution, crystallization from vapor, and crystallization from a molten form.

The method of the "crystallization from a solution" include, for example, a concentration method, a slow cooling method, a reaction method (diffusion method, electrolysis method), a hydrothermal growth method, a fusing agent method, and so forth. The solvents to be used include, for example, aromatic hydrocarbons (e.g., benzene, toluene, xylene, etc.), halogenated hydrocarbons (e.g., dichloromethane, chloroform, etc.), saturated hydrocarbons (e.g., hexane, heptane, cyclohexane, etc.), ethers (e.g., diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, etc.), nitrites (e.g., acetonitrile, etc.), ketones (e.g., acetone, etc.), sulfoxides (e.g., dimethylsulfoxide, etc.), acid amides (e.g., N,N-dimethylformamide, etc.), esters (e.g., ethyl acetate, etc.), alcohols (e.g., methanol, ethanol, isopropyl alcohol, etc.), water, and so forth. These solvents may be used singly or in a mixture of two or more kinds at appropriate ratios (e.g., 1:1 to 1:100).

The method of the "crystallization from vapor" includes, for example, a gasification method (sealed tube method, gas stream method), a gas phase reaction method, a chemical transportation method, and so forth.

The method of the "crystallization from a molten form" includes, for example, a normal freezing method (pulling-up method, temperature gradient method, Bridgman method), a zone melting method (zone leveling method, float zone method), a special growth method (VLS method, liquid phase epitaxis method), and so forth.

Examples of the crystal of (R)-lansoprazole or (S)-lansoprazole to be used as a starting material in the crystal production method of the present invention include the following:

- (1) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 5.88, 4.70, 4.35, 3.66 and 3.48 Angstrom in an X-ray powder diffraction of wet crystal;
- (2) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom in an X-ray powder diffraction of wet crystal;
- (3) a mixture of the crystals of the aforementioned (1) and (2); and
- (4) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

The enantiomeric excess of (R)-lansoprazole or (S)-lansoprazole to be applied to the crystal production method of the present invention is, for example, not less than about 80% ee, preferably not less than about 90% ee.

More preferable (R)-lansoprazole does not contain (S)-lansoprazole substantially. By "does not contain substan-

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tially" is meant (R)-lansoprazole containing (S)-lansoprazole in 0-3%, preferably 0-1%. More preferably, (S)-lansoprazole does not contain (R)-lansoprazole substantially. By "does not contain substantially" here is meant (S)-lansoprazole containing (R)-lansoprazole in 0-3%, preferably 0-1%.

It is preferable that (R)-lansoprazole or (S)-lansoprazole obtained by the above-mentioned production method be subjected to the step to be mentioned below for improving the optical purity.

For an increased optical purity of the (R)-lansoprazole or (S)-lansoprazole obtained by the above-mentioned production method, for example, the method described in JP-A-11-508590 (WO 97/02261) or a method analogous thereto, or the following method [1] or [2] is employed.

[1] A crystal of (R)-lansoprazole is selectively crystallized from a solution containing (R)-lansoprazole in a greater amount than (S)-lansoprazole and the precipitated crystal is separated to give a crystal of (R)-lansoprazole substantially free of (S)-lansoprazole.

[2] A crystal of (S)-lansoprazole is selectively crystallized from a solution containing (S)-lansoprazole in a greater amount than (R)-lansoprazole and the precipitated crystal is separated to give a crystal of (S)-lansoprazole substantially free of (R)-lansoprazole.

It is also possible to separate the precipitated crystal after the above-mentioned [1] or [2] and subject the crystal to recrystallization once or more.

The methods for "selective crystallization" include, for example, a method of stirring a solution, a method of adding a seed crystal to a solution, a method of changing the temperature of a solution, a method of changing the solvent composition of a solution, a method of decreasing the liquid amount of a solution, or a method consisting of two or more of these methods in combination and the like.

The "method of stirring a solution" includes, for example, stirring a solution containing one of (R)-lansoprazole and (S)-lansoprazole in a greater amount than the other at about -80° C. to 120° C., preferably at about -20° C. to 60° C., for about 0.01 to 100 hours, preferably for about 0.1 to 10 hours.

The "method of adding a seed crystal to a solution" include, for example, adding (1) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 5.88, 4.70, 4.35, 3.66 and 3.48 Angstrom; (2) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 8.33, 6.63, 5.86 and 4.82 Angstrom; (3) a mixture of the crystals of the aforementioned (1) and (2) or (4) in a solution, a solid that transforms to the aforementioned (1)-(3) (e.g., a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom; a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 8.86, 8.01, 6.58, 5.91, 5.63, 5.02 and 4.48 Angstrom; a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 8.37, 4.07, 5.65, 5.59, 5.21, 4.81 and 4.21 Angstrom; a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 11.68, 6.78, 5.85, 5.73, 4.43, 4.09, 3.94, 3.90, 3.69, 3.41 and 3.11 Angstrom, etc.) to a solution containing one of (R)-lansoprazole and (S)-lansoprazole in a greater amount than the other as a seed crystal.

The "method of changing the temperature of a solution" includes, for example, changing the temperature of a solution containing one of (R)-lansoprazole and (S)-lansopra-



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zole in a greater amount than the other, preferably by cooling (e.g., lower the liquid temperature by 5-100° C.).

The "method of changing the solvent composition of a solution" includes, for example, adding water, a low polar organic solvent (e.g., esters, ethers, aromatic hydrocarbons, hydrocarbons, halogenated hydrocarbons or a mixture of two or more of these etc.) or a mixture of two or more of these to a solution containing one of (R)-lansoprazole and (S)-lansoprazole in a greater amount than the other.

The "method of decreasing the liquid amount of a solution" includes, for example, distilling away or evaporating the solvent from a solution containing one of (R)-lansoprazole and (S)-lansoprazole in a greater amount than the other and the like.

Of these, preferred are:

- (i) a method of stirring a solution,
- (ii) a method comprising a method of stirring a solution and a method of adding a seed crystal to a solution,
- (iii) a method comprising a method of stirring a solution and a method of changing the temperature of a solution,
- (iv) a method comprising a method of stirring a solution and a method of changing the solvent composition of a solution,
- (v) a method comprising a method of stirring a solution and a method of decreasing the liquid amount of a solution,
- (vi) a method comprising a method of stirring a solution, a method of changing the temperature of a solution and a method of adding a seed crystal to a solution,
- (vii) a method comprising a method of stirring a solution, a method of changing the solvent composition of a solution and a method of adding a seed crystal to a solution,
- (viii) a method comprising a method of stirring a solution, a method of decreasing the liquid amount of a solution and a method of adding a seed crystal to a solution,
- (ix) a method comprising a method of stirring a solution, a method of changing the temperature of a solution and a method of changing the solvent composition of a solution,
- (x) a method comprising a method of stirring a solution, a method of changing the temperature of a solution, a method of changing the solvent composition of a solution and a method of adding a seed crystal to a solution,
- (xi) a method comprising a method of stirring a solution, a method of changing the temperature of a solution and a method of decreasing the liquid amount of a solution, and
- (xii) a method comprising a method of stirring a solution, a method of changing the temperature of a solution, a method of decreasing the liquid amount of a solution and a method of adding a seed crystal to a solution.

The precipitated crystal can be separated by, for example, filtration, centrifugation and the like.

The thus-obtained crystal may be used as it is, or dried, where necessary, or may be subjected to a recrystallization step, where necessary.

The "drying" includes, for example, vacuum drying, through-flow drying, drying by heating, air drying and the like.

When, for example, (R)-lansoprazole or (S)-lansoprazole obtained by asymmetric synthesis is used, it is applied to the method of the above-mentioned [1] or [2], or where necessary, recrystallization once or more times to reduce the amount of analogous materials (e.g., 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole and/or 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfonyl]-1H-benzimidazole, etc.) in the precipitated crystals.

To be specific, the obtained crystal or a dry crystal thereof is dissolved in a solvent (e.g., water, esters, ketones, phenols, alcohols, ethers, aromatic hydrocarbons, amides, sulfoxides,

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hydrocarbons, nitrites, halogenated hydrocarbons, pyridines or a mixture of two or more of these), applied to a dehydration step where necessary, and crystallized.

The "dehydrating" is performed by a conventional dehydration method, such as a concentration method, a method using a dehydrating agent [e.g., anhydrous magnesium sulfate, anhydrous sodium sulfate, molecular sieve (trade name)] and the like.

Examples of the "crystallization" method include the aforementioned crystallization method.

The crystal obtained after the above-mentioned recrystallization is exemplified by:

- (1) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 5.88, 4.70, 4.35, 3.66 and 3.48 Angstrom in an X-ray powder diffraction of wet crystal,
- (2) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom in an X-ray powder diffraction of wet crystal,
- (3) a mixture of the crystals of the aforementioned (1) and (2), and
- (4) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

The amount of the analogous materials in the crystal is less than 1 wt %, preferably less than 0.4 wt %.

The crystal precipitated in the recrystallization step can be separated by, for example, filtration, centrifugation and the like.

The thus-obtained crystal may be used as it is, or dried, where necessary, or may be subjected to a second recrystallization step, where necessary.

The "drying" is done by a method similar to the above-mentioned "drying".

To be specific, the obtained crystal is dissolved in a solvent (e.g., water, esters, ketones, phenols, alcohols, ethers, aromatic hydrocarbons, amides, sulfoxides, hydrocarbons, nitrites, halogenated hydrocarbons, pyridines or a mixture of two or more of these etc.), applied to a dehydration step where necessary, crystallized, separated and dried.

The "dehydrating" is performed by a method such as the above-mentioned "dehydration method".

Examples of the "crystallization" method include the aforementioned crystallization method.

The crystal obtained in the above-mentioned second recrystallization step is exemplified by a crystal of (R)- or (S)-lansoprazole, which shows an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

The crystal obtained in the second recrystallization step may be separated by, for example, filtration, centrifugation and the like.

The separated crystal can be dried by, for example, vacuum drying, through-flow drying, drying by heating, air drying and the like.

The "esters" include, for example, methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, ethyl formate and the like.

The "ketones" include, for example, acetone, methyl ethyl ketone, methyl isopropyl ketone, methyl butyl ketone, methyl isobutyl ketone and the like.

The "phenols" include, for example, anisole and the like.

The "alcohols" include, for example, methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 2-methyl-1-propanol, pentanol, 3-methyl-1-butanol, 2-methoxyethanol, 2-ethoxyethanol, ethylene glycol and the like.

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The "ethers" include, for example, t-butyl methyl ether, diethyl ether, 1,1-diethoxypropane, 1,1-dimethoxypropane, 2,2-dimethoxypropane, isopropyl ether, tetrahydrofuran, methyltetrahydrofuran and the like.

The "aromatic hydrocarbons" include, for example, chlorobenzene, toluene, xylene, cumene and the like.

The "amides" include, for example, formamide, N,N-dimethylacetamide, N,N-dimethylformamide, N-methylpyrrolidone and the like.

The "sulfoxides" include, for example, dimethylsulfoxide and the like.

The "hydrocarbons" include, for example, propane, hexane, pentane, octane, isooctane and the like.

The "nitriles" include, for example, acetonitrile and the like.

The "halogenated hydrocarbons" include, for example, chloroform, dichloromethane, dichloroethene, trichloroethene and the like.

The "pyridines" include, for example, pyridine and the like.

The crystal obtained by crystallization by the above-mentioned method and dry crystal thereof do not substantially contain the other enantiomer.

(R)-Lansoprazole or (S)-lansoprazole obtained by the above-mentioned various methods is applied to the crystal production method of the present invention.

The crystal production method of the present invention is described in detail in the following.

(1) Step for Crystallization at a Temperature of About 0° C. to About 35° C. from C<sub>1-4</sub> Alkyl Acetate Solution Containing (R)-lansoprazole or (S)-lansoprazole at a Concentration of About 0.1 g/mL to About 0.5 g/mL

First, (R)-lansoprazole or (S)-lansoprazole is made to be present in C<sub>1-4</sub> alkyl acetate at a concentration of about 0.1 g/mL to about 0.5 g/mL (preferably about 0.1 g/mL to about 0.35 g/mL, more preferably about 0.2 g/mL to about 0.3 g/mL, particularly preferably about 0.25 g/mL to about 0.28 g/mL).

For example, an excess C<sub>1-4</sub> alkyl acetate is added to (R)-lansoprazole or (S)-lansoprazole, and the mixture is heated where necessary at about 30° C. to 60° C. to dissolve same and concentrated under reduced pressure to achieve a given concentration (about 0.1 g/mL to about 0.5 g/mL).

As used herein, the concentration is measured according to an area comparison method with a standard product solution using high performance liquid chromatography. The measurement method is explained in detail in the following.

#### Measurement Conditions

Column: Shiseido CAPCELL PAK C18 SG120 5 μm 4.6×250 mm

Column Temp.: 25° C.

Mobile phase: H<sub>2</sub>O:CH<sub>3</sub>CN:Et<sub>3</sub>N=50:50:1 (adjusted to pH 7.0 with phosphoric acid)

Flow rate: 1.0 mL/min.

Inject. Vol.: 10 μl

Wavelength: 285 nm

#### Sample Preparation

Standard solution: standard product (about 75 mg) is precisely weighed and mobile phase is added to make the amount 100 mL.

Sample solution: mobile phase is added to ethyl acetate solution (1 mL) to make the amount 100 mL.

#### Concentration Measurement Method

Standard solution (10 μl) and sample solution (10 μl) are tested by liquid chromatography under the aforementioned HPLC conditions and peak area A<sub>S</sub> of (R)-lansoprazole or (S)-lansoprazole in the Standard solution, and the peak area

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A<sub>T</sub> of (R)-lansoprazole or (S)-lansoprazole in the sample solution are measured by automatic integration, based on which the concentration of (R)-lansoprazole or (S)-lansoprazole is calculated from the following formula:

$$(A_T/A_S) \times (W_S/1000)$$

W<sub>S</sub>: standard product sample amount (mg)

The concentration can be made to fall within the optimal range for the selected solvent, wherein the state of saturation or per-saturation (R)-lansoprazole or (S)-lansoprazole is preferable for crystallization.

The C<sub>1-4</sub> alkyl acetate includes methyl acetate, ethyl acetate, propyl acetate, butyl acetate and the like, of which preferably used are ethyl acetate and propyl acetate.

The crystallization is performed by standing or stirring a C<sub>1-4</sub> alkyl acetate solution containing the above-mentioned (R)-lansoprazole or (S)-lansoprazole according to a method known per se at a crystallization temperature of about 0° C. to about 35° C.

The lower limit of crystallization temperature is preferably about 10° C., more preferably about 15° C., most preferably about 20° C. The upper limit of crystallization temperature is preferably about 30° C. Particularly, crystallization temperature is preferably about 20° C. to about 30° C.

The crystallization time is about 30 minutes to about 10 hours, preferably about 30 minutes to about 4 hours, particularly preferably about 1 hour to about 2 hours.

In this step, a seed crystal may be added to the solution. Examples of the seed crystal include one that may be added to the solution before or during dropwise addition of C<sub>5-8</sub> hydrocarbon to be mentioned below.

This step is carried out in an atmosphere or under an inert gas atmosphere, or in an inert gas stream. As the "inert gas", one usable for dropwise addition of C<sub>5-8</sub> hydrocarbon to be mentioned below is employed.

The crystal obtained by this step can be separated by a method such as filtration, centrifugation and the like.

The separated crystal may be washed, where necessary, with a (1:0-1:10) mixture of C<sub>1-4</sub> alkyl acetate-C<sub>5-8</sub> hydrocarbon, and the like. The C<sub>1-4</sub> alkyl acetate here is exemplified by those mentioned above, and the C<sub>5-8</sub> hydrocarbon is exemplified by those mentioned below. The separated crystal can be dried by, for example, vacuum drying, through-flow drying, drying by heating, air drying and the like.

The crystal obtained by this step is superior in preservation stability and can be used as the pharmaceutical product to be mentioned below. By the following step (2), the objective crystal superior in preservation stability can be obtained in a high yield.

(2) Step for Adding Dropwise C<sub>5-8</sub> Hydrocarbon in an Amount of Not More Than 7 Times the Amount of the C<sub>1-4</sub> Alkyl Acetate Solution at the Same Temperature After Step (1)

By applying this step to the crystal obtained by the above-mentioned step (1) after separation or without separation, the crystal can be obtained in greater amounts.

This step is preferably applied after precipitation of the crystal in the above-mentioned step (1). It is preferably applied after precipitation of a crystal in at least about 20 wt %, more preferably about 30 wt % to about 90 wt %, particularly preferably about 50 wt % to about 90 wt %, of (R)-lansoprazole or (S)-lansoprazole added as a starting material.

The crystallization temperature in this step is the same as in step (1).

Examples of C<sub>5-8</sub> hydrocarbon include straight chain or branched C<sub>5-8</sub> aliphatic hydrocarbon, such as pentane, iso-

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pentane, neopentane, hexane, isohexane, 3-methylpentane, neohexane, 2,3-dimethylbutane, heptane, 2-methylhexane, 3-methylhexane, 3-ethylpentane, 2,2-dimethylpentane, 2,3-dimethylpentane, 2,4-dimethylpentane, 3,3-dimethylpentane, 2,2,3-trimethylbutane, octane, isooctane and the like, and C<sub>7-8</sub> aromatic hydrocarbon, such as toluene, xylene and the like. Preferably, heptane and straight chain C<sub>5-8</sub> aliphatic hydrocarbon such as hexane and the like, are used.

The amount of dropwise addition of C<sub>5-8</sub> hydrocarbon is not more than 7 times, preferably not more than 5 times, more preferably 1 to 3 times, the amount of the C<sub>1-4</sub> alkyl acetate solution containing (R)-lansoprazole or (S)-lansoprazole in step (1).

The dropwise addition includes sequential dropwise addition of almost the same amount over, for example, about 15 minutes to about 4 hours (preferably about 1 hour to about 2 hours) while standing or stirring the solution.

The temperature during dropwise addition is preferably adjusted to the above-mentioned crystallization temperature.

In this step, a seed crystal may be added to the solution before or during the dropwise addition of C<sub>5-8</sub> hydrocarbon.

The seed crystal includes, for example,

- (1) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 5.88, 4.70, 4.35, 3.66 and 3.48 Angstrom,
- (2) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom X-ray powder diffraction,
- (3) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom,
- (4) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 8.86, 8.01, 6.58, 5.91, 5.63, 5.02 and 4.48 Angstrom,
- (5) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 8.37, 4.07, 5.65, 5.59, 5.21, 4.81 and 4.21 Angstrom,
- (6) a crystal showing an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings (d) of 11.68, 6.78, 5.85, 5.73, 4.43, 4.09, 3.94, 3.90, 3.69, 3.41 and 3.11 Angstrom,
- (7) a mixture of two or more crystals from the aforementioned (1)-(6) and
- (8) a solid that transforms into the aforementioned (1)-(6) in a solution.

After the dropwise addition, the mixture may be stood or stirred on demand for about 1 hour to about 3 hours.

This step is applied in an atmosphere or under an inert gas atmosphere, or in an inert gas stream. The "inert gas" includes, for example, nitrogen, helium, neon, argon and the like.

The crystal obtained by this step can be separated by filtration, centrifugation and the like.

The separated crystal may be washed, where necessary, with a C<sub>1-4</sub> alkyl acetate—C<sub>5-8</sub> hydrocarbon (1:0.1:10) mixture and the like. As used herein, the C<sub>1-4</sub> alkyl acetate and C<sub>5-8</sub> hydrocarbon are exemplified by those mentioned above. The separated crystal can be dried by, for example, vacuum drying, through-flow drying, drying by heating, air drying and the like.

The obtained crystal can be analyzed generally by crystal analysis by X-ray diffraction. The orientation of the crystal can be determined by a mechanical method, optical method and the like.

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The crystal obtained by the above-mentioned production method (step (1) alone, or step (2) after step (1)) has the following melting start temperature by DSC measurement (temperature rise rate 0.5° C./min). As used herein, the "melting start temperature" refers to the temperature at which crystals start to melt when heated under, for example, the DSC measurement conditions to be mentioned below. The crystal has the melting start temperature of not less than about 131° C., preferably about 131° C. to about 137° C., more preferably about 132° C. to about 135° C., most preferably about 133° C. to about 135° C., particularly preferably about 135° C. For example, the melting start temperature of the crystal obtained in the above-mentioned step (1) can be about 135° C. In addition, the melting start temperature of the crystal obtained by step (2) after applying the above-mentioned step (1) can be about 132° C. to about 135° C.

The melting start temperature of the crystal obtained by a conventional method is less than about 131° C. For example, the melting start temperature of the crystal obtained by the method of Reference Example 3 mentioned below was about 125° C. to about 130° C.

The crystal having a melting start temperature of not less than about 131° C., which is obtained by the production method of the present invention, has extremely superior preservation stability as compared to the crystal having a melting start temperature of less than about 131° C., which is obtained by a prior art method. In the stability test (40° C.—one month residual ratio, 60° C.—one month residual ratio) to be mentioned below, for example, the crystal obtained by the production method of the present invention showed a residual ratio of not less than 99%, but the ratio of the crystal obtained by a conventional method was less than 94%. Moreover, the crystal obtained by a conventional method showed noticeable coloring during preservation.

The crystal having a melting start temperature of not less than about 131° C., which is obtained by the production method of the present invention, has such superior preservation stability and can be used advantageously as a pharmaceutical product, as compared to the crystal having a melting start temperature of less than about 131° C., which is obtained by a prior art method.

The crystal of (R)-lansoprazole or (S)-lansoprazole obtained by the crystal production method of the present invention is useful as a pharmaceutical product because it shows excellent antiulcer activity, gastric acid secretion-inhibiting action, mucosa-protecting action, anti-*Helicobacter pylori* action, etc., and because it is of low toxicity. The dry crystal of (R)-lansoprazole or (S)-lansoprazole is stabler than a precipitated crystal (wet crystal) of (R)-lansoprazole or (S)-lansoprazole, and when it is used as a pharmaceutical product, a dry crystal of (R)-lansoprazole or (S)-lansoprazole is preferably used.

The crystal or dry crystal obtained by the method of the present invention is useful for mammals (e.g., humans, monkeys, sheep, bovines, horses, dogs, cats, rabbits, rats, mice, etc.) in the treatment and prevention of digestive ulcer (e.g., gastric ulcer, duodenal ulcer, stomach ulcer, Zollinger-Ellison syndrome, etc.), gastritis, reflux esophagitis, NUD (non-ulcer dyspepsia), gastric cancer (inclusive of gastric cancer caused by promotion of interleukin-1 $\beta$  production due to genetic polymorphism of interleukin-1) and gastric MALT lymphoma; *Helicobacter pylori* eradication; suppression of upper gastrointestinal hemorrhage due to digestive ulcer, acute stress ulcer and hemorrhagic gastritis; suppression of upper gastrointestinal hemorrhage due to invasive stress (stress from major surgery necessitating intensive management after surgery, and from cerebral vascular disorder, head trauma, multiple organ failure and extensive burn necessitating intensive treatment); treatment and pre-



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vention of ulcer caused by a nonsteroidal anti-inflammatory agent; treatment and prevention of hyperacidity and ulcer due to postoperative stress; pre-anesthetic administration and the like. For eradication of *Helicobacter pylori*, the crystal or dry crystal obtained by the method of the present invention and antibiotic penicillins (e.g., amoxicillin etc.) and antibiotic erythromycins (e.g., clarithromycin, etc.) are preferably used.

For the above-mentioned various pharmaceutical uses, the crystal of (R)-lansoprazole is preferably used.

The crystal of the present invention can be safely administered orally or non-orally (e.g., topical, rectal and intravenous administration, etc.), as such or in the form of pharmaceutical compositions formulated with a pharmacologically acceptable carrier, e.g., tablets (including sugar-coated tablets and film-coated tablets), powders, granules, capsules (including soft capsules), orally disintegrating tablets, liquids, injectable preparations, suppositories, sustained-release preparations and patches, in accordance with a commonly known method.

The content of the crystal of the present invention in the pharmaceutical composition of the present invention is about 0.01 to 100 wt % relative to the entire composition. Varying depending on subject of administration, route of administration, target disease etc., its dose is normally about 0.5 to 1,500 mg/day, preferably about 5 to 150 mg/day, based on the active ingredient, when, for example, it is orally administered as an antiulcer agent to an adult human (60 kg). The crystal of the present invention may be administered once daily or in 2 to 3 divided portions per day.

Pharmacologically acceptable carriers that may be used to produce the pharmaceutical composition of the present invention include various organic or inorganic carrier substances in common use as pharmaceutical materials, including excipients, lubricants, binders, disintegrants, water-soluble polymers and basic inorganic salts for solid preparations; and solvents, dissolution aids, suspending agents, isotonicity agents, buffers and soothing agents for liquid preparations. Other ordinary pharmaceutical additives such as preservatives, antioxidants, coloring agents, sweetening agents, souring agents, bubbling agents and flavorings may also be used as necessary.

Such "excipients" include, for example, lactose, sucrose, D-mannitol, starch, cornstarch, crystalline cellulose, light silicic anhydride, titanium oxide and the like.

Such "lubricants" include, for example, magnesium stearate, sucrose fatty acid esters, polyethylene glycol, talc, stearic acid and the like.

Such "binders" include, for example, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, crystalline cellulose,  $\alpha$ -starch, polyvinylpyrrolidone, gum arabic powder, gelatin, pullulan, low-substituted hydroxypropyl cellulose and the like.

Such "disintegrants" include (1) crosslinked povidone, (2) what is called super-disintegrants such as crosslinked carmellose sodium (FMC-Asahi Chemical) and carmellose calcium (Gotoku Yakuhin), (3) carboxymethyl starch sodium (e.g., product of Matsutani Chemical), (4) low-substituted hydroxypropyl cellulose (e.g., product of Shin-Etsu Chemical), (5) cornstarch, and so forth. Said "crosslinked povidone" may be any crosslinked polymer having the chemical name 1-ethenyl-2-pyrrolidinone homopolymer, including, what is called, polyvinylpyrrolidone (PVPP) and 1-vinyl-2-pyrrolidinone homopolymer, and is exemplified by Colidon CL (produced by BASF), Polyplasdon XL (produced by ISP), Polyplasdon XL-10 (produced by ISP), Polyplasdon INF-10 (produced by ISP) and the like.

Such "water-soluble polymers" include, for example, ethanol-soluble water-soluble polymers [e.g., cellulose

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derivatives such as hydroxypropyl cellulose (hereinafter also referred to as HPC), polyvinylpyrrolidone etc.], ethanol-insoluble water-soluble polymers [e.g., cellulose derivatives such as hydroxypropylmethyl cellulose (hereinafter also referred to as HPMC), methyl cellulose and carboxymethyl cellulose sodium, sodium polyacrylate, polyvinyl alcohol, sodium alginate, guar gum etc.] and the like.

Such "basic inorganic salts" include, for example, basic inorganic salts of sodium, potassium, magnesium and/or calcium. Preferred are basic inorganic salts of magnesium and/or calcium. More preferred are basic inorganic salts of magnesium. Such basic inorganic salts of sodium include, for example, sodium carbonate, sodium hydrogen carbonate, disodium hydrogenphosphate, etc. Such basic inorganic salts of potassium include, for example, potassium carbonate, potassium hydrogen carbonate, etc. Such basic inorganic salts of magnesium include, for example, heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydro-talcite [ $\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O}$ ], alumina hydroxide magnesium, and so forth. Among others, preferred is heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, etc. Such basic inorganic salts of calcium include, for example, precipitated calcium carbonate, calcium hydroxide and the like.

Such "solvents" include, for example, water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil, olive oil and the like.

Such "dissolution aids" include, for example, polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate and the like.

Such "suspending agents" include, for example, surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and monostearic glycerol; and hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose.

Such "isotonicity agents" include, for example, glucose, D-sorbitol, sodium chloride, glycerol, D-mannitol and the like.

Such "buffers" include, for example, buffer solutions of phosphates, acetates, carbonates, citrates and the like.

Such "soothing agents" include, for example, benzyl alcohol and the like.

Such "preservatives" include, for example, p-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and the like.

Such "antioxidants" include, for example, sulfites, ascorbic acid,  $\alpha$ -tocopherol and the like.

Such "coloring agents" include, for example, foodcolors such as Food Color Yellow No. 5, Food Color Red No. 2 and Food Color Blue No. 2; and food lake colors, Bengal and the like.

Such "sweetening agents" include, for example, saccharin sodium, dipotassium glycyrrhetinate, aspartame, stevia, thaumatin and the like.

Such "souring agents" include, for example, citric acid (citric anhydride), tartaric acid, malic acid and the like.

Such "bubbling agents" include, for example, sodium bicarbonate and the like.

Such "flavorings" may be synthetic substances or naturally occurring substances, and include, for example, lemon, lime, orange, menthol, strawberry and the like.

The crystal of the present invention may be prepared as a preparation for oral administration in accordance with a commonly known method, by, for example, compression-

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shaping it in the presence of an excipient, a disintegrant, a binder, a lubricant or the like, and subsequently coating it as necessary by a commonly known method for the purpose of taste masking, enteric dissolution or sustained release. For an enteric preparation, an intermediate layer may be provided by a commonly known method between the enteric layer and the drug-containing layer for the purpose of separation of the two layers.

For preparing the crystal of the present invention as an orally disintegrating tablet, available method include, for example, a method in which a core containing crystalline cellulose and lactose is coated with the crystal of the present invention and a basic inorganic salt, and is further coated with a coating layer containing a water-soluble polymer, to give a composition, which is coated with an enteric coating layer containing polyethylene glycol, further coated with an enteric coating layer containing triethyl citrate, still further coated with an enteric coating layer containing polyethylene glycol, and still yet further coated with mannitol, to give fine granules, which are mixed with additives and shaped. The above-mentioned "enteric coating layer" includes, for example, aqueous enteric polymer substrates such as cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate, hydroxymethyl cellulose acetate succinate, methacrylic acid copolymers [e.g., Eudragit L30D-55 (trade name; produced by Rohm), Colicoat MAE30DP (trade name; produced by BASF), Polykid PA30 (trade name; produced by San-yo Chemical) etc.], carboxymethylethyl cellulose and shellac; sustained-release substrates such as methacrylic acid polymers [e.g., Eudragit NE30D (trade name), Eudragit RL30D (trade name), Eudragit RS30D (trade name), etc.]; water-soluble polymers; plasticizers such as triethyl citrate, polyethylene glycol, acetylated monoglycerides, triacetin and castor oil; and mixtures of one or more thereof. The above-mentioned "additive" includes, for example, water-soluble sugar alcohols (e.g., sorbitol, mannitol, multitol, reduced starch saccharides, xylitol, reduced paratinose, erythritol, etc.), crystalline cellulose [e.g. Ceolas KG 801, Avicel PH 101, Avicel PH 102, Avicel PH 301, Avicel PH 302, Avicel RC-591 (crystalline cellulose carmellose sodium) etc.], low-substituted hydroxypropyl cellulose [e.g., LH-22, LH-32, LH-23, LH-33 (Shin-Etsu Chemical) and mixtures thereof etc.] etc.; binders, souring agents, bubbling agents, sweetening agents, flavorings, lubricants, coloring agents, stabilizers, excipients, disintegrants etc. are also used.

The crystal of the present invention may be used in combination with 1 to 3 other active ingredients.

Such "other active ingredients" include, for example, anti-*Helicobacter pylori* activity substances, imidazole compounds, bismuth salts, quinolone compounds, and so forth. Of these substances, preferred are anti-*Helicobacter pylori* action substances, imidazole compounds etc. Such "anti-*Helicobacter pylori* action substances" include, for example, antibiotic penicillins (e.g., amoxicillin, benzylpenicillin, piperacillin, mecillinam, etc.), antibiotic cefems (e.g., cefixime, cefaclor, etc.), antibiotic macrolides (e.g., erythromycin, clarithromycin, etc.), antibiotic tetracyclines (e.g., tetracycline, minocycline, streptomycin, etc.), antibiotic aminoglycosides (e.g., gentamicin, amikacin, etc.), imipenem, and so forth. Of these substances, preferred are antibiotic penicillins, antibiotic macrolides etc. Especially preferred is a triple therapy of an antibiotic penicillins, an antibiotic macrolide and the crystal of (R)-lansoprazole or (S)-lansoprazole. Such "imidazole compounds" include, for example, metronidazole, miconazole, etc. Such "bismuth salts" include, for example, bismuth acetate, bismuth citrate, etc. Such "quinolone compounds" include, for example, ofloxacin, ciprofloxacin, etc.

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Such "other active ingredients" and the crystal of the present invention may also be used in combination as a mixture prepared as a single pharmaceutical composition [e.g., tablets, powders, granules, capsules (including soft capsules), liquids, injectable preparations, suppositories, sustained-release preparations, etc.], in accordance with a commonly known method, and may also be prepared as separate preparations and administered to the same subject simultaneously or at a time interval.

While the present invention is explained in detail in the following by referring to Reference Examples and Examples, the present invention is not limited by these Examples.

The X-ray powder diffraction was measured using X-ray Diffractometer RINT Ultima+ (Rigaku).

The melting start temperature was measured using DSC (differential scanning calorimeter SEIKO DSC220C) under the following measurement conditions.

DSC Measurement Conditions;

temperature range: room temperature to 220° C.

temperature rise rate: 0.5° C./min.

sample container: aluminum pan (without cover)

atmosphere: nitrogen gas (100 mL/min)

Enantiomeric excess (% ee) was measured by high performance liquid chromatography using an optically active column for the following conditions (A).

The amounts of sulfide and sulfone present were measured by high performance liquid chromatography using an optically active column for the following conditions (A) or high performance liquid chromatography under the conditions (B).

High Performance Liquid Chromatography Conditions (A);

Column: CHIRALCEL OD (4.6×250 mm; DAICEL CHEMICAL INDUSTRIES, LTD.)

Mobile phase: hexane/ethanol=90/10

Flow rate: 1.0 mL/min

Detection: UV 285 nm

High Performance Liquid Chromatography Conditions (B);

Column: CAPCELL PAK C18 SG120 5 µm 4.6×250 mm (Shiseido Co., Ltd.)

Mobile Phase: acetonitrile:water:triethylamine mixture (50:50:1) adjusted to pH 7.0 with phosphoric acid

Flow rate: 1.0 mL/min

Detection: UV 285 nm

#### Reference Example 1

Production of Solution Containing (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole by Asymmetric Oxidation

2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole monohydrate (6 kg, 16.2 mol) was dried in vacuo at 80° C. for 21 hours to give 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole (5.73 kg, water content 0.0364%). 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole (5.00 kg, 14.1 mol, containing water 1.82 g), toluene (25 L), water (13.18 g, 0.732 mol, as total water content 0.833 mol) and (+)-diethyl tartrate (531 mL, 3.10 mol) were mixed under a nitrogen gas stream. Titanium(IV) isopropoxide (414 mL, 1.40 mol) was added at 50-60° C. under a nitrogen gas stream, and the mixture was stirred at the same temperature for 30 min. Diisopropylethylamine (815 mL, 4.68 mol) was added under a nitrogen gas stream at 15-25° C., and cumene hydroperoxide (7.65 L, content 82%, 42.7 mol) was added at -10° C. to 5° C. and the mixture was stirred at -8° C. to 2° C. for 3 hours to allow reaction.



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The analysis results of the reaction mixture by high performance liquid chromatography (conditions (A)) are as follows.

The enantiomeric excess of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole in the reaction mixture was 96.9% ee.

As a result of the analysis of the reaction mixture by high performance liquid chromatography (conditions (B)), analogous materials in the reaction mixture were found to be sulfide 1.0% and sulfone 1.7% alone.

#### Reference Example 2

Purification Method of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole

(1) To the reaction mixture obtained in the above-mentioned Reference Example 1 was added 30% aqueous sodium thiosulfate solution (13.5 kg) under a nitrogen gas stream, and the remaining cumene hydroperoxide was decomposed. The mixture was concentrated under reduced pressure until the liquid amount became about 25 L. Heptane-t-butyl methyl ether (heptane:t-butyl methyl ether=1:1, 20 L) was added dropwise while maintaining the mixture at 0-10° C. and heptane (70 L) was added dropwise. The precipitated crystals were separated, and washed with cooled t-butyl methyl ether-toluene (t-butyl methyl ether:toluene=4:1, 5 L).

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), the enantiomeric excess of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole in the crystal was found to be 98.3% ee.

As a result of the analysis of the reaction mixture by high performance liquid chromatography (conditions (B)), analogous materials in the reaction mixture were found to be sulfide 0.45% and sulfone 1.8% alone.

(2) A suspension of the wet crystal obtained in the above-mentioned (1) in acetone (20 L) was added dropwise to a mixture of acetone (7.5 L) and water (37.5 L), and water (52.5 L) was added. The precipitated crystals were separated and washed with cooled acetone-water (acetone:water=1:3, 5 L) and water (6.5 L).

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), the enantiomeric excess of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole in the crystal was found to be 100% ee.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (B)), analogous materials in the crystal were found to be sulfide 0.19% and sulfone 0.08% alone.

(3) The wet crystal obtained in the above-mentioned (2) was suspended in ethyl acetate (50 L) and magnesium sulfate (2.5 kg) was added. Magnesium sulfate was separated and the residue was washed with ethyl acetate (3.5 L). After addition of triethylamine (250 mL), the mixture was concentrated under reduced pressure until the liquid amount became about 10 L. To the concentrate were added methanol (2.5 L), about 12.5% aqueous ammonia (25.5 L, about 50° C.) and t-butyl methyl ether (24.5 L, about 50° C.) for partitioning. About 12.5% aqueous ammonia (12 L, about 50° C.) was added to the organic layer and the mixture was partitioned (this step was repeated once). The aqueous layers were combined, ethyl acetate (24.5 L) was added, and acetic acid was added dropwise at not more than 20° C. to adjust the pH to about 8. After partitioning, the aqueous layer was extracted with ethyl acetate (24.5 L). The organic layers were combined

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and washed with about 20% brine (24.5 L). After addition of triethylamine (250 mL), the organic layer was concentrated under reduced pressure. Acetone (5.55 L) was added to the concentrate and the mixture was concentrated under reduced pressure. The concentrate was dissolved in acetone (10 L) and the solution was added dropwise to a mixture of acetone (5 L) and water (25 L). Water (20 L) was added dropwise to the obtained mixture. The precipitated crystal was separated and successively washed with cooled acetone-water (1:3, 4 L) and water (13 L).

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), the enantiomeric excess of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole in the crystal was found to be 100% ee.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (B)), analogous materials in the crystal were found to be sulfide 0.018% and sulfone 0.016% alone.

#### Reference Example 3

Purification Method of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole

The wet crystal obtained by the method of the above-mentioned Reference Example 2 was dissolved in ethyl acetate (43 L). The separated aqueous layer was partitioned and the obtained organic layer was concentrated under reduced pressure until the liquid amount became about 19 L. Ethyl acetate (48 L) was added to the concentrate, and the mixture was concentrated under reduced pressure until the liquid amount became about 19 L. Ethyl acetate (48 L) and activated carbon (360 g) were added to the concentrate and the mixture was stirred and the activated carbon was filtered off. The filtrate was concentrated under reduced pressure until the liquid amount became about 19 L. Heptane (150 L) was added dropwise to the concentrate at about 40° C. The mixture was stirred at the same temperature for about 30 minutes and the crystal was separated and washed with ethyl acetate-heptane (1:8, 8 L, about 40° C.) and dried to give the title compound (4.5 kg).

The analysis results of the crystal by X-ray powder diffraction are as follows.

The crystal showed an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), analogous materials in the crystal were found to be sulfone 0.02% alone, and other analogous materials such as sulfide and the like were not found. The enantiomeric excess of (R)-lansoprazole in the crystal was 100% ee.

The melting start temperature of the crystal was 127.5° C.

#### Reference Example 4

Production of (S)-lansoprazole

(1) 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole (50.0 g, 0.14 mol, containing water 20 mg), toluene (250 mL), water (130 mg, 0.0072 mol, total water content 0.0083 mol) and (-)-diethyl tartrate (5.31 mL, 0.031 mol) were mixed under a nitrogen atmosphere. Titanium(IV) isopropoxide (4.14 mL, 0.014 mol) was added to the mixture at 50° C. and the mixture was stirred at 50-55° C. for 1 hour under a nitrogen atmosphere. Diisopropylethylamine (8.13 mL,

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0.047 mol) was added to the obtained mixture under a nitrogen atmosphere and cooling, and cumene hydroperoxide (76.50 mL, content 82%, 0.42 mol) was added at -10° C. to 0° C. The mixture was stirred at -5° C. to 5° C. for 3.5 hours to give a reaction mixture.

As a result of the analysis of the reaction mixture by high performance liquid chromatography (conditions (A)), the enantiomeric excess of (S)-lansoprazole in the reaction mixture was 96.5% ee.

As a result of the analysis of the reaction mixture by high performance liquid chromatography (conditions (B)), analogous materials in the reaction mixture were found to be sulfone 1.90% and sulfide 1.50% alone.

(2) To the reaction mixture obtained in the above-mentioned (1) was added 30% aqueous sodium thiosulfate solution (180 mL) under a nitrogen gas stream, and the remaining cumene hydroperoxide was decomposed. The mixture was partitioned, and water (50 mL), heptane (150 mL), t-butyl methyl ether (200 mL) and heptane (300 mL) were successively added to the obtained organic layer to allow crystallization. The crystal was separated and washed with t-butyl methyl ether-toluene (t-butyl methyl ether: toluene=4:1, 45 mL) to give (S)-lansoprazole having interplanar spacings(d) in the following X-ray powder diffraction, as a wet crystal.

As a result of the analysis of the crystal by X-ray powder diffraction, the wet crystal showed an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 5.88, 4.70, 4.35, 3.66 and 3.48 Angstrom.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), the enantiomeric excess of the crystal was 100% ee.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (B)), the analogous material in the crystal was sulfone 0.72% and other analogous materials such as sulfide and the like were not found.

(3) A suspension of the wet crystal obtained in the above-mentioned (2) in acetone (220 mL) was added dropwise to a mixture of acetone (75 mL) and water (370 mL), and then water (520 mL) was added. The precipitated crystal was separated and washed with acetone-water (acetone: water=1:3, 44 mL) and water (130 mL) to give a wet crystal of (S)-lansoprazole having interplanar spacings(d) in the following X-ray powder diffraction.

As a result of the analysis of the wet crystal by X-ray powder diffraction, the crystal showed an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 8.33, 6.63, 5.86 and 4.82 Angstrom.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), the enantiomeric excess of the crystal was 100% ee.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (B)), analogous materials such as sulfone, sulfide and the like were not found.

#### Reference Example 5

##### Production of (S)-lansoprazole

The wet crystal (containing the title compound 35.37 g, content of analogous materials: 0%, enantiomeric excess: 100% ee) obtained according to Reference Example 4 was dissolved in ethyl acetate (340 mL). The aqueous layer was separated by partitioning and the obtained organic layer was concentrated under reduced pressure until the liquid amount became about 100 mL. Ethyl acetate (400 mL) and activated

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carbon (3 g) were added to the concentrate and the mixture was stirred. The activated carbon was removed by filtration. The filtrate was concentrated under reduced pressure until the liquid amount became about 100 mL. Heptane (1000 mL) was added dropwise to the concentrate at about 40° C. The mixture was stirred at the same temperature for about 30 minutes, and the crystal was separated and washed with ethyl acetate-heptane (1:8, 63 mL, about 40° C.). The crystal was dried to give the title compound (35.08 g, yield: 99.2%).

As a result of the analysis of the crystal by X-ray powder diffraction, the crystal showed an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), analogous materials such as sulfone, sulfide and the like were not found in the crystal. The enantiomeric excess of (S)-lansoprazole in the crystal was 100% ee.

The melting start temperature of the crystal was 127.0° C.

#### Reference Example 6

The crystal (1.5 g, 4.06 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in ethyl acetate (30 mL) and concentrated to 6 mL under reduced pressure at an outer temperature of about 25° C. Heptane (24 mL) was added dropwise at about -5° C. for about 30 minutes. After stirring for about 2.5 hours, the precipitated crystal was separated and dried to give the title compound (1.46 g, yield: 97.3%).

As a result of the analysis of the crystal by X-ray powder diffraction, the crystal showed an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), analogous materials such as sulfone, sulfide and the like were not found in the crystal. The enantiomeric excess of (R)-lansoprazole in the crystal was 100% ee.

The melting start temperature of the crystal was 130.0° C.

#### Reference Example 7

The crystal (1.5 g, 4.06 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in ethyl acetate (30 mL) and concentrated to 20 mL under reduced pressure at an outer temperature of about 25° C. Heptane (90 mL) was added dropwise at about 25° C. for about 30 minutes. After stirring for about 2.5 hours, the precipitated crystal was separated and dried to give the title compound (1.40 g, yield: 93.3%).

As a result of the analysis of the crystal by X-ray powder diffraction, the crystal showed an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), analogous materials such as sulfone, sulfide and the like were not found in the crystal. The enantiomeric excess of (R)-lansoprazole in the crystal was 100% ee.

The melting start temperature of the crystal was 128.5° C.

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## EXAMPLE 1

Production Method of High Melting Point Crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole

The wet crystal obtained according to the method of the above-mentioned Reference Example 2 was dissolved in ethyl acetate (50 L). The mixture was partitioned and the organic layer was concentrated under reduced pressure until the liquid amount became about 25 L. Ethyl acetate (30 L) was added to the concentrate, and the mixture was concentrated under reduced pressure until the liquid amount became about 15 L. Ethyl acetate (30 L) and activated carbon (150 g) were added to the concentrate. The activated carbon was removed and the mixture was washed with ethyl acetate (1.5 L). The filtrate was concentrated under reduced pressure until the concentration of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole became about 0.28 g/mL (12.5 L). The mixture was stirred under a nitrogen gas stream, at about 25° C. for about 2 hours, and after confirmation of crystal precipitation, heptane (25 L) was dropwise added over about 1.5 hours, and the mixture was stirred for about 1.5 hours. The precipitated crystal was separated, washed with ethyl acetate:heptane=1:5, 6 L) and dried to give the title compound (3.66 kg, yield: 70% based on 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole).

As a result of the analysis of the crystal by X-ray powder diffraction, the crystal showed an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), the enantiomeric excess of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole in the crystal was 100% ee.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (B)), the analogous material was sulfone 0.01% alone, and sulfide and the like were not found. The melting start temperature of the crystal was 134.0° C.

## EXAMPLE 2

The crystal (3 g, 8.12 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in ethyl acetate (12 mL) at about 50° C. and the solution was stirred at about 25° C. for about 6 hours. The precipitated crystal was separated, washed with ethyl acetate:heptane (ethyl acetate:heptane=1:5, 3 mL) and dried to give the title compound (1.55 g, yield: 52%).

As a result of the analysis of the crystal by X-ray powder diffraction, the crystal showed an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), analogous materials such as sulfone, sulfide and the like were not

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found. The enantiomeric excess of (R)-lansoprazole in the crystal was 100% ee.

The melting start temperature of the crystal was 135.0° C.

## EXAMPLE 3

The crystal (1.5 g, 4.06 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in n-propyl acetate (30 mL) and concentrated to 6 mL under reduced pressure at an outer temperature of about 25° C. After stirring for about 2.5 hours, the precipitated crystal was separated and dried to give the title compound (0.94 g, yield: 63%).

The melting start temperature of the crystal was 134.5° C.

## EXAMPLE 4

The crystal (3.0 g, 8.12 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in ethyl acetate (12 mL) at about 50° C. The mixture was stirred at about 25° C. for about 2.5 hours, and after confirmation of crystal precipitation, heptane (60 mL) was dropwise added over about 15 minutes. The precipitated crystal was separated, washed with ethyl acetate:heptane (ethyl acetate:heptane=1:5, 3 mL) and dried to give the title compound (2.84 g, yield: 95%).

The melting start temperature of the crystal was 133.5° C.

## EXAMPLE 5

The crystal (3.0 g, 8.12 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in ethyl acetate (12 mL) at about 50° C. The mixture was stirred at about 25° C. for about 2 hours, and after confirmation of crystal precipitation, hexane (24 mL) was dropwise added over about 20 minutes. The precipitated crystal was separated, washed with ethyl acetate:hexane (ethyl acetate:hexane=1:5, 3 mL) and dried to give the title compound.

The melting start temperature of the crystal was 133.5° C.

## EXAMPLE 6

The crystal (2.0 g, 5.41 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in n-propyl acetate (30 mL) at about 30° C. The mixture was concentrated to 8 mL under reduced pressure at an outer temperature of about 25° C. After stirring for about 1.5 hours, crystal precipitation was confirmed, and heptane (16 mL) was dropwise added over about 20 minutes. The precipitated crystal was separated, washed twice with n-propyl acetate:heptane (n-propyl acetate:heptane=1:5, 6 mL) and dried to give the title compound (1.86 g, yield: 93%).

The melting start temperature of the crystal was 134.0° C.

## EXAMPLE 7

The crystal (2.0 g, 5.41 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in i-propyl acetate (40 mL) at about 35° C. The mixture was concentrated to 8 mL under reduced pressure at an outer temperature of about 35° C. After stirring for about 1.5 hours, crystal precipitation was confirmed, and heptane (16 mL) was dropwise added over about 20 minutes. The precipitated crystal was separated, washed

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twice with i-propyl acetate-heptane (i-propyl acetate:heptane=1:5, 6 mL) and dried to give the title compound (1.89 g, yield: 95%).

The melting start temperature of the crystal was 133.0° C.

## EXAMPLE 8

The crystal (2.0 g, 5.41 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in n-butyl acetate (40 mL) at about 35° C. The mixture was concentrated to 8 mL under reduced pressure at an outer temperature of about 35° C. After stirring for about 1 hour, crystal precipitation was confirmed, and heptane (16 mL) was dropwise added over about 20 minutes. The precipitated crystal was separated, washed twice with n-butyl acetate-heptane (n-butyl acetate:heptane=1:5, 6 mL) and dried to give the title compound (1.87 g, yield: 93%).

The melting start temperature of the crystal was 133.0° C.

## EXAMPLE 9

The crystal (2.0 g, 5.41 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in methyl acetate (15 mL). The mixture was concentrated to 8 mL under reduced pressure at an outer temperature of about 25° C. After stirring for about 1.5 hours, crystal precipitation was confirmed, and heptane (16 mL) was dropwise added over about 20 minutes. The precipitated crystal was separated, washed twice with methyl acetate-heptane (methyl acetate:heptane=1:5, 6 mL) and dried to give the title compound (1.71 g, yield: 86%).

The melting start temperature of the crystal was 134.0° C.

## EXAMPLE 10

The wet crystal obtained according to the method of the above-mentioned Reference Example 4 was dissolved in ethyl acetate (50 L). The mixture was partitioned and the organic layer was concentrated under reduced pressure until the liquid amount became about 27 L. Ethyl acetate (30 L) was added to the concentrate, and the mixture was concentrated under reduced pressure until the liquid amount became about 16 L. Ethyl acetate (30 L) and activated carbon (150 g) were added to the concentrate. The activated carbon was removed and the mixture was washed with ethyl acetate (1.5 L). The filtrate was concentrated under reduced pressure until the concentration of (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole became about 0.27 g/mL (12.5 L). After stirring at about 25° C. for about 2 hours under a nitrogen gas stream, crystal precipitation was confirmed, and heptane (25 L) was dropwise added over about 1.5 hours. The mixture was stirred for about 1.5 hours. The precipitated crystal was separated, washed with ethyl acetate-heptane (ethyl acetate:heptane=1:5, 6 L) and dried to give the title compound (3.76 kg, yield: 72% based on 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole).

As a result of the analysis of the crystal by X-ray powder diffraction, the crystal showed an X-ray powder diffraction analysis pattern having characteristic peaks at interplanar spacings(d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

As a result of the analysis of the crystal by high performance liquid chromatography (conditions (A)), the enantiomeric excess of (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole in the crystal was 100% ee.

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As a result of the analysis of the crystal by high performance liquid chromatography (conditions (B)), analogous materials in the crystal, such as sulfone, sulfide and the like were not found.

The melting start temperature of the crystal was 133.5° C.

## EXAMPLE 11

The crystal (1.5 g, 4.06 mmol) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole was dissolved in ethyl acetate (30 mL). The mixture was concentrated to 6 mL under reduced pressure at an outer temperature of about 25° C. The mixture was stirred for about 2 hours at the same temperature, and precipitation of the crystal was confirmed. Heptane (24 mL) was dropwise added over about 30 minutes. The mixture was stirred for about 2.5 hours, and the precipitated crystal was separated and dried to give the title compound (1.46 g, yield: 97.3%).

The melting start temperature of the crystal was 133.5° C.

Experimental Example: Stability Test (Relationship Between Melting Start Temperature and Stability)

Various (R)-lansoprazole crystals obtained in the above-mentioned Reference Examples and Examples were subjected to a stability test at 60° C. for one month. The partial results are shown in Table 1 below.

TABLE 1

production method	melting start temperature	60° C. one month residual ratio
present invention (1) (Example 2)	135.0° C.	100%
present invention (2) (Example 1)	134.0° C.	99.7%
present invention (3) (Example 6)	134.0° C.	99.2%
conventional method (A) (Reference Example 6)	130.0° C.	93.8%
conventional method (B) (Reference Example 3)	127.5° C.	89.8%

The crystal obtained by the method of the present invention shows a residual ratio of not less than 99% in a 60° C. one month stability test. The crystal obtained by a conventional method shows a residual ratio decreased to about 90-94%.

The crystal of (R)-lansoprazole was subjected to a 40° C. one month stability test. The partial results are shown in the following Table 2.

TABLE 2

production method	present invention (Example 11)	conventional method (Reference Example 7)
melting start temperature initial	133.5° C.	128.5° C.
appearance	almost white	almost white
content	99.5%	99.6%
analogous material content	0.2%	0.1%
40° C. one month		
appearance	almost white	brown
content	99.7%	93.8%
analogous material content	0.2%	4.6%



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By the method of the present invention, decomposition was not found in the 40° C. one month stability test, but the appearance was degraded, the content decreased and the analogous material content increased by the conventional method.

In FIG. 1, the appearance of a crystal (Example 1) having a melting start temperature of about 134° C. and a crystal (Reference Example 6) having a melting start temperature of about 130° C. before stability test and after stability tests (40° C. 2 weeks, 50° C. 2 weeks and 60° C. 2 weeks) is shown. The crystal having a melting start temperature of about 134° C. did not show changes in the appearance but the crystal having a melting start temperature of about 130° C. showed appreciably degraded appearance.

From the foregoing results, it is apparent that there exists a clear relationship between melting start temperature and stability in the case of the crystals of (R)-lansoprazole and (S)-lansoprazole, and that the crystal having a melting start temperature of not lower than about 131° C. is stable but the crystal having a melting start temperature of less than about 131° C. is unstable.

#### Formulation Example 1

#### Production of Capsule

Capsules (15 mg) were obtained according to the charge amount-1 in the following Table 3 and the following method (in Table 4, amounts per capsule are shown). (1) The crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (hereinafter to be referred to as compound A) obtained in Example 1 and the ingredients (3) to (6) were thoroughly mixed to give a dusting powder. In a centrifugal fluidized coating granulator was charged (2) Nonpareil and the above-mentioned dusting powder was coated while spraying an aqueous solution of (7) hydroxypropyl cellulose in purified water. The spherical granules were dried in vacuo at 40° C. for 16-20 hours and passed through a sieve (600 μm, 1180 μm) to give base granules. The base granules were placed in a roll flow type coating machine and coated with a suspension of (8) methacrylic acid copolymer LD-(12) polysorbate 80 in purified water. The coated granules were passed through a sieve (710 μm, 1400 μm) and dried in vacuo at 40° C. for 16-20 hours to give enteric coated granules. To the enteric coated granules were added (13) talc and (14) light silicic anhydride and mixed granules were produced in a tumbler mixer. The mixed granules were filled in (17) HPMC Capsule No. 2 by a capsule filling machine to give 15 mg capsules.

By controlling the amount to be filled of the above-mentioned mixed granules, 20 mg and 10 mg capsules were produced.

TABLE 3

Charge amount-1	
ingredients	15 mg capsule
[base granule]	
(1) compound A	450.0 g
(2) sucrose · starch spherical granule (Nonpareil)	1650.0
(3) magnesium carbonate	336.0
(4) purified sucrose	897.0
(5) cornstarch	546.0

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TABLE 3-continued

Charge amount-1	
ingredients	15 mg capsule
(6) low-substituted hydroxypropyl cellulose	600.0
(7) hydroxypropyl cellulose	21.0
purified water	1029.0
subtotal	4500.0 g
[enteric coated granule]	
base granule	3600.0 g
(8) methacrylic acid copolymer LD (Eudragit L30D-55 <sup>TR</sup> )	535.2
(9) talc	160.8
(10) macrogol 6000	52.8
(11) titanium oxide	52.8
(12) polysorbate 80	24.0
purified water	2054.4
subtotal	4425.6 g
[mixed granule]	
enteric coated granule	3688.0 g
(13) talc	6.0
(14) light silicic anhydride	2.0
subtotal	3696.0 g
[capsule]	
mixed granule	924.0 g
(15) HPMC Capsule No. 2	5000.0 cap.

TABLE 4

Formulation per capsule	
ingredients	15 mg capsule
[base granule]	
(1) compound A	15.00 mg
(2) sucrose · starch spherical granule (Nonpareil)	55.00
(3) magnesium carbonate	11.20
(4) purified sucrose	29.90
(5) cornstarch	18.20
(6) low-substituted hydroxypropyl cellulose	20.00
(7) hydroxypropyl cellulose	0.70
subtotal	150.00 mg
[enteric coated granule]	
base granule	150.00 mg
(8) methacrylic acid copolymer LD (Eudragit L30D-55 <sup>TR</sup> )	22.30
(9) talc	6.70
(10) macrogol 6000	2.20
(11) titanium oxide	2.20
(12) polysorbate 80	1.00
subtotal	184.40 mg



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TABLE 4-continued

<u>Formulation per capsule</u>		
ingredients		15 mg capsule
<u>[mixed granule]</u>		
	enteric coated granule	184.40 mg
(13)	talc	0.30
(14)	light silicic anhydride	0.10
		<hr/>
	subtotal	184.80 mg
<u>[capsule]</u>		
	mixed granule	184.80 mg
(15)	HPMC Capsule No. 2	62.00
		<hr/>
	subtotal	246.80 mg

## Formulation Example 2

## Production of Capsule

Capsules (15 mg) were obtained according to the charge amount-2 in the following Table 5 and the following method (in Table 6, amounts per capsule are shown). (1) Compound A and the ingredients (3) to (6) were thoroughly mixed to give a main drug dusting powder. The ingredients (7) to (9) were thoroughly mixed to give a cover coating agent. In a centrifugal fluidized coating granulator was charged (2) Nonpareil and the above-mentioned main drug dusting powder and the cover coating agent were successively coated while spraying an aqueous solution of (10) hydroxypropyl cellulose in purified water. The spherical granules were dried in vacuo at 40° C. for 16-20 hours and passed through a sieve (600  $\mu$ m, 1180  $\mu$ m) to give base granules. The base granules were placed in a roll flow type coating machine and coated with a suspension of (11) methacrylic acid copolymer LD-(15) polysorbate 80 in purified water. The coated granules were passed through a sieve (710  $\mu$ m, 1400  $\mu$ m) and dried in vacuo at 40° C. for 16-20 hours to give enteric-coated granules. To the enteric coated granules were added (16) talc and (17) light silicic anhydride and mixed granules were produced in a tumbler mixer. The mixed granules were filled in (18) HPMC Capsule No. 2 by a capsule filling machine to give 15 mg capsules.

TABLE 5

<u>Charge amount-2</u>		
<u>ingredients</u>		
<u>[base granule]</u>		
(1)	compound A	450.0 g
(2)	sucrose · starch spherical granule (Nonpareil)	1650.0
(3)	magnesium carbonate	336.0
(4)	purified sucrose	597.0
(5)	cornstarch	300.0
(6)	low-substituted hydroxypropyl cellulose	354.0
(7)	purified sucrose	300.0
(8)	cornstarch	246.0
(9)	low-substituted hydroxypropyl cellulose	246.0
(10)	hydroxypropyl cellulose	21.0
	purified water	1029.0
	subtotal	4500.0 g
<u>[enteric coated]</u>		

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TABLE 5-continued

<u>Charge amount-2</u>		
ingredients		
<u>granule]</u>		
	base granule	3600.0 g
(11)	methacrylic acid copolymer LD (Eudragit L30D-55 <sup>TR</sup> )	535.2
(12)	talc	160.8
(13)	macrogol 6000	52.8
(14)	titanium oxide	52.8
(15)	polysorbate 80	24.0
	purified water	2054.4
	subtotal	4425.6 g
<u>[mixed granule]</u>		
	enteric coated granule	3688.0 g
(16)	talc	6.0
(17)	light silicic anhydride	2.0
	subtotal	3696.0 g
<u>[capsule]</u>		
	mixed granule	924.0 g
(18)	HPMC Capsule No. 2	5000.0 cap.

TABLE 6

<u>Formulation per capsule</u>		
ingredients		15 mg capsule
<u>[base granule]</u>		
(1)	compound A	15.0 mg
(2)	sucrose · starch spherical granule (Nonpareil)	55.0
(3)	magnesium carbonate	11.2
(4)	purified sucrose	19.9
(5)	cornstarch	10.0
(6)	low-substituted hydroxypropyl cellulose	11.8
(7)	purified sucrose	10.0
(8)	cornstarch	8.2
(9)	low-substituted hydroxypropyl cellulose	8.2
(10)	hydroxypropyl cellulose	0.7
subtotal		150.0 mg
<u>[enteric coated granule]</u>		
	base granule	150.0 mg
(11)	methacrylic acid copolymer LD (Eudragit L30D-55 <sup>TR</sup> )	22.3
(12)	talc	6.7
(13)	macrogol 6000	2.2
(14)	titanium oxide	2.2
(15)	polysorbate 80	1.0
subtotal		184.4 mg
<u>[mixed granule]</u>		
	enteric coated granule	184.4 mg
(16)	talc	0.3
(17)	light silicic anhydride	0.1
subtotal		184.8 mg

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TABLE 6-continued

<u>Formulation per capsule</u>	
ingredients	15 mg capsule
<u>[capsule]</u>	
(18) mixed granule	184.8 mg
HPMC Capsule No. 2	62.0
subtotal	246.8 mg

## INDUSTRIAL APPLICABILITY

According to the production method of the present invention, a crystal of (R)-lansoprazole or (S)-lansoprazole superior in preservation stability can be produced efficiently on an industrial large scale.

This application is based on patent application No. 2000-367757 filed in Japan, the contents of which are hereby incorporated by reference.

The invention claimed is:

1. A method for producing a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, which comprises crystallizing at a temperature of about 0° C. to about 35° C. from a C<sub>1-4</sub> alkyl acetate solution containing (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole at a concentration of about 0.1 g/mL to about 0.5 g/mL.

2. A method for producing a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole,

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which comprises crystallizing at a temperature of about 0° C. to about 35° C. from a C<sub>1-4</sub> alkyl acetate solution containing (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole at a concentration of about 0.1 g/mL to about 0.5 g/mL, and adding dropwise to the C<sub>1-4</sub> alkyl acetate solution, at the same temperature, C<sub>5-8</sub> hydrocarbon in an amount of not more than 7 times the amount of the C<sub>1-4</sub> alkyl acetate solution.

3. The method of claim 1, wherein the crystallization temperature is about 20° C. to about 30° C.

4. The method of claim 1, wherein the crystallization is conducted for about 30 minutes to about 4 hours.

5. The method of claim 1, wherein the C<sub>1-4</sub> alkyl acetate is ethyl acetate or propyl acetate.

6. The method of claim 2, wherein the C<sub>5-8</sub> hydrocarbon is added in an amount of not more than 5 times the amount of the C<sub>1-4</sub> alkyl acetate solution.

7. The method of claim 2, wherein the C<sub>5-8</sub> hydrocarbon is heptane or hexane.

8. The method of claim 2, wherein the C<sub>5-8</sub> hydrocarbon is added dropwise over about 15 minutes to about 4 hours.

9. A crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole having a melting start temperature of not lower than about 131° C.

10. The crystal of claim 9, wherein the melting start temperature is about 135° C.

11. The method of claim 2, wherein the crystallization temperature is about 20° C. to about 30° C.

12. The method of claim 2, wherein the crystallization is conducted for about 30 minutes to about 4 hours.

13. The method of claim 2, wherein the C<sub>1-4</sub> alkyl acetate is ethyl acetate or acetate.

\* \* \* \* \*

# **EXHIBIT E**

US007790755B2

(12) **United States Patent**  
**Akiyama et al.**(10) **Patent No.:** **US 7,790,755 B2**  
(45) **Date of Patent:** **Sep. 7, 2010**(54) **CONTROLLED RELEASE PREPARATION**(75) Inventors: **Yohko Akiyama**, Osaka (JP); **Takashi Kurasawa**, Osaka (JP); **Hiroto Bando**, Osaka (JP); **Naoki Nagahara**, Osaka (JP)(73) Assignee: **Takeda Pharmaceutical Company Limited**, Osaka (JP)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1022 days.

(21) Appl. No.: **10/531,069**(22) PCT Filed: **Oct. 15, 2003**(86) PCT No.: **PCT/JP03/13155**§ 371 (c)(1),  
(2), (4) Date: **Apr. 11, 2005**(87) PCT Pub. No.: **WO2004/035020**PCT Pub. Date: **Apr. 29, 2004**(65) **Prior Publication Data**

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(30) **Foreign Application Priority Data**Oct. 16, 2002 (JP) ..... 2002-301876  
Mar. 12, 2003 (JP) ..... 2003-066336(51) **Int. Cl.****A61K 31/4439** (2006.01)  
**C07D 401/02** (2006.01)(52) **U.S. Cl.** ..... **514/339**; 546/273.7(58) **Field of Classification Search** ..... 546/273.7;  
514/339

See application file for complete search history.

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(57) **ABSTRACT**

A controlled release preparation wherein the release of active ingredient is controlled, which releases an active ingredient for an extended period of time by staying or slowly migrating in the gastrointestinal tract, is provided by means such as capsulating a tablet, granule or fine granule wherein the release of active ingredient is controlled and a gel-forming polymer. Said tablet, granule or fine granule has a release-controlled coating-layer formed on a core particle containing an active ingredient.

**9 Claims, No Drawings**

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## CONTROLLED RELEASE PREPARATION

This application is the National Phase filing of International Patent Application No. PCT/JP03/013155, filed Oct. 15, 2003.

## TECHNICAL FIELD

The present invention relates to a controlled release preparation, in particular a capsule comprising a tablet, granule or fine granule wherein the release of active ingredient is controlled and a gel-forming polymer which delays the migration speed in the gastrointestinal tract.

## BACKGROUND ART

An oral formulation is a dosage form which is used most frequently among pharmaceutical agents. Lots of preparations for oral administration wherein the drug efficacy thereof is sustained with the administration of once or twice a day have been developed from the viewpoint of improving QOL in these years. The compound having a kinetics of sustained drug efficacy with the administration of once or twice a day is tried to synthesize in the synthetic stage of compound itself, while quite a lot of attempts to modify the kinetics are made with designing controlled release preparation by contriving formulation. As the dosage form of oral controlled release preparation, various release-controlled systems such as a release control by a release-controlled coating-layer or a diffusion control of compound by a matrix, a release control of compound by erosion of matrix (base material), a pH-dependent release control of compound and a time-dependent release control wherein the compound is released after a certain lag time, are developed and applied. It is considered that a further extension of sustainability becomes possible by combining the above-mentioned release-controlled system with a control of migration speed in the gastrointestinal tract.

The preparation containing a medicament having an acid-labile property as an active ingredient such as a benzimidazole compound having a proton pump inhibitor (hereinafter sometimes referred to as PPI) action needs to be enteric-coated. That is, a composition containing a benzimidazole compound having a proton pump inhibitor action is needed to disintegrate rapidly in the small intestine, so the composition is preferred to formulate into a granule or fine granule which has a broader surface area than a tablet and is easy to disintegrate or dissolve rapidly. In the case of a tablet, it is desirable to reduce the size of tablet (for example, see JP-A 62-277322).

After administered orally, the tablet, granule or fine granule migrates through gastrointestinal tract with releasing an active ingredient to stomach, duodenum, jejunum, ileum and colon sequentially. And in the meantime, the active ingredient is absorbed at the each absorption site. A controlled release preparation is designed to control the absorption by delaying the release of active ingredient in some way. It is considered that a further extension of sustainability becomes possible by combining a release-controlled system with a function to control the migration speed in gastrointestinal tract such as adhesion, floatability etc. These prior arts are disclosed in WO 01/89483, JP-A 2001-526213, U.S. Pat. Nos. 6,274,173, 6,093,734, 4,045,563, 4,686,230, 4,873,337, 4,965,269, 5,021,433 and the like.

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## DISCLOSURE OF INVENTION

(Object of the Invention)

An object of the present invention is to provide a controlled release preparation wherein the release of active ingredient of drug is controlled, which releases an active ingredient for an extended period of time with staying or slowly migrating in the gastrointestinal tract.

## SUMMARY OF THE INVENTION

That is, the present invention provides:

(1) A capsule comprising a tablet, granule or fine granule and a gel-forming polymer wherein a release of an active ingredient is controlled;

(2) The capsule according to the above-mentioned (1), wherein the release of active ingredient is controlled by a release-controlled coating-layer formed on a core particle containing an active ingredient;

(3) The capsule according to the above-mentioned (2), wherein the release-controlled coating-layer contains a pH-dependently soluble polymer;

(4) The capsule according to the above-mentioned (2), wherein the release-controlled coating-layer is a diffusion-controlled layer;

(5) The capsule according to the above-mentioned (1), wherein the release of active ingredient is controlled by dispersing an active ingredient into a release-controlled matrix composing tablet, granule or fine granule;

(6) The capsule according to the above-mentioned (3) or (4), wherein the tablet, granule or fine granule in which the release of active ingredient is controlled has a disintegrant layer containing disintegrant formed on the core particle containing an active ingredient and a release-controlled coating-layer formed on said disintegrant layer, and the release of active ingredient is initiated after a certain lag time;

(7) The capsule according to any one of the above-mentioned (3) to (6), wherein the tablet, granule or fine granule in which the release of active ingredient is controlled is coated with a gel-forming polymer;

(8) The capsule according to the above-mentioned (7) which further contains a gel-forming polymer;

(9) The capsule according to any one of the above-mentioned (1) to (7), which comprises two kinds of tablet, granule or fine granule having different release properties of active ingredient;

(10) The capsule according to the above-mentioned (9), which comprises a tablet, granule or fine granule having an enteric coat that releases an active ingredient at the pH of about 5.5 and a tablet, granule or fine granule having a release-controlled coating-layer that releases an active ingredient at the pH of about 6.0 or above;

(11) The capsule according to the above-mentioned (1), (7) or (8), wherein the gel-forming polymer is a polymer whose viscosity of 5% aqueous solution is about 3,000 mPa·s or more at 25° C.;

(12) The capsule according to the above-mentioned (1), (7) or (8), wherein the gel-forming polymer is a polymer having molecular weight of 400,000 to 10,000,000;

(13) The capsule according to any one of the above-mentioned (2) to (4) or (6), wherein the release-controlled coating-layer is a layer containing one or more kinds of polymeric substances selected from the group consisting of hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, carboxymethylethyl cellulose, methyl methacrylate-methacrylic acid copolymer, methacrylic acid-ethyl acrylate

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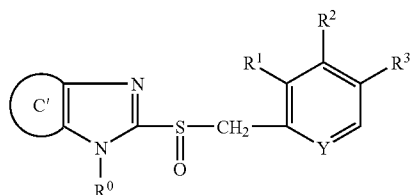
copolymer, ethyl acrylate-methyl methacrylate-trimethylammoniummethyl methacrylate chloride copolymer, methyl methacrylate-ethyl acrylate copolymer, methacrylic acid-methyl acrylate-methyl methacrylate copolymer, hydroxypropyl cellulose acetate succinate and polyvinyl acetate phthalate;

(14) The capsule according to the above-mentioned (13), wherein the release-controlled coating-layer is comprised of 2 or more kinds of layers;

(15) The capsule according to the above-mentioned (1), wherein the release-controlled granule or fine granule has a particle size of about 100-1,500  $\mu\text{m}$ ;

(16) The capsule according to the above-mentioned (1), wherein the active ingredient is a proton pump inhibitor (PPI);

(17) The capsule according to (16), wherein the PPI is an imidazole compound represented by the formula (I'):



wherein ring C' is an optionally substituted benzene ring or an optionally substituted aromatic monocyclic heterocyclic ring, R<sup>0</sup> is a hydrogen atom, an optionally substituted aralkyl group, acyl group or acyloxy group, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are the same or different and are a hydrogen atom, an optionally substituted alkyl group, an optionally substituted alkoxy group or an optionally substituted amino group, and Y represents a nitrogen atom or CH; or a salt thereof or an optically active isomer thereof;

(18) The capsule according to the above-mentioned (17), wherein the imidazole compound is lansoprazole;

(19) The capsule according to the above-mentioned (17), wherein PPI is an optically active R-isomer of lansoprazole;

(20) The capsule according to any one of the above-mentioned (1), (7) or (8), wherein the gel-forming polymer is one or more kinds of substances selected from the group consisting of polyethylene oxide (PEO, molecular weight: 400,000-10,000,000), hydroxypropylmethyl cellulose (HPMC), carboxymethyl cellulose (CMC-Na), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose and carboxyvinyl polymer;

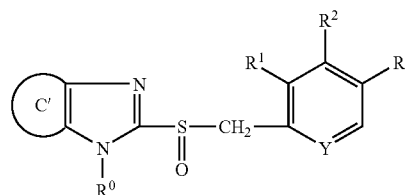
(21) The capsule according to any one of the above-mentioned (1), (7) or (8), wherein the gel-forming polymer is polyethylene oxide (molecular weight: 400,000-10,000,000);

(22) The capsule according to the above-mentioned (1) or (8), wherein the gel-forming polymer is added as a powder, fine granule or granule;

(23) The capsule according to the above-mentioned (3), wherein the pH-dependently soluble polymer is methyl methacrylate-methacrylic acid copolymer;

(24) A tablet, granule or fine granule wherein the release of active ingredient is controlled, said tablet, granule or fine granule comprising a core particle containing an imidazole compound represented by the formula (I'):

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(I')

wherein ring C' is an optionally substituted benzene ring or an optionally substituted aromatic monocyclic heterocyclic ring, R<sup>0</sup> is a hydrogen atom, an optionally substituted aralkyl group, acyl group or acyloxy group, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are the same or different and are a hydrogen atom, an optionally substituted alkyl group, an optionally substituted alkoxy group or an optionally substituted amino group, and Y represents a nitrogen atom or CH; or a salt thereof or an optically active isomer thereof as an active ingredient, and

a pH-dependently soluble release-controlled coating-layer which comprises one kind of polymeric substance or a mixture of two or more kinds of polymeric substances having different release properties selected from the group consisting of hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, carboxymethylethyl cellulose, methyl methacrylate-methacrylic acid copolymer, methacrylic acid-ethyl acrylate copolymer, methacrylic acid-methyl acrylate-methyl methacrylate copolymer, hydroxypropyl cellulose acetate succinate, polyvinyl acetate phthalate and shellac, and said polymeric substance is soluble in the pH range of 6.0 to 7.5;

(25) The tablet, granule or fine granule according to the above-mentioned (24), wherein the pH-dependently soluble release-controlled coating-layer is formed on an intermediate layer which is formed on a core particle;

(26) The capsule comprising the tablet, granule or fine granule according to the above-mentioned (24);

(27) The capsule comprising the tablet, granule or fine granule according to the above-mentioned (24) and an enteric-coated tablet, granule or fine granule containing a compound represented by the formula (II);

(28) The tablet, granule or fine granule according to the above-mentioned (24), wherein the active ingredient is lansoprazole;

(29) The tablet, granule or fine granule according to the above-mentioned (24), wherein the active ingredient is an optically active R-isomer of lansoprazole;

(30) The tablet, granule or fine granule according to the above-mentioned (24), wherein the active ingredient is an optically active S-isomer of lansoprazole;

(31) The tablet, granule or fine granule according to the above-mentioned (24), wherein the active ingredient is a derivative of lansoprazole;

(32) The tablet, granule or fine granule according to the above-mentioned (24), wherein the active ingredient is a derivative of optically active R-isomer of lansoprazole;

(33) The tablet, granule or fine granule according to any one of the above-mentioned (24), (25) or (28) to (32), comprising having an enteric coat on the core particle containing an active ingredient, a disintegrant layer containing disintegrant on said enteric coat and a release-controlled coating-layer on said disintegrant layer;

(34) The tablet, granule or fine granule according to any one of the above-mentioned (28) to (33), which is coated with a gel-forming polymer;

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(35) An extended release capsule comprising the tablet, granule or fine granule according to any one of the above-mentioned (28) to (32) and a gel-forming polymer;

(36) A tablet, granule or fine granule according to the above-mentioned (24) wherein the release of active ingredient is controlled by two or more kinds of release-controlled coating-layers, and the outermost release-controlled coating-layer is soluble at higher pH than the inner release-controlled coating-layer;

(37) The tablet, granule or fine granule according to the above-mentioned (36), wherein the inner release-controlled coating-layer is soluble in the pH range of 6.0-7.0 and the outermost release-controlled coating-layer is soluble at the pH of 7.0 or above;

(38) The tablet, granule or fine granule according to the above-mentioned (36), wherein the inner release-controlled coating-layer is soluble in the pH range of 6.5-7.0 and the outermost release-controlled coating-layer is soluble at the pH of 7.0 or above;

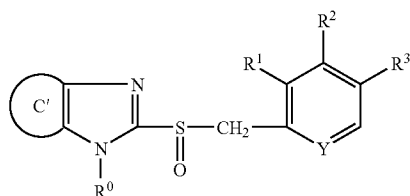
(39) The tablet, granule or fine granule according to the above-mentioned (36), wherein the thickness of the outermost release-controlled coating-layer is 100  $\mu\text{m}$  or less;

(40) The granule or fine granule according to the above-mentioned (36), wherein the release-controlled granule or fine granule has a particle size of about 100-1,500  $\mu\text{m}$ ;

(41) A capsule comprising

(i) a tablet, granule or fine granule in which the release of active ingredient is controlled; said tablet, granule or fine granule comprises

a core particle containing an imidazole compound represented by the formula (I'):



wherein ring C' is an optionally substituted benzene ring or an optionally substituted aromatic monocyclic heterocyclic ring,  $R^0$  is a hydrogen atom, an optionally substituted aralkyl group, acyl group or acyloxy group,  $R^1$ ,  $R^2$  and  $R^3$  are the same or different and are a hydrogen atom, an optionally substituted alkyl group, an optionally substituted alkoxy group or an optionally substituted amino group, and Y represents a nitrogen atom or CH; or a salt thereof or an optically active isomer thereof as an active ingredient, and

a pH-dependently soluble release-controlled coating-layer which comprises one kind of polymeric substance or a mixture of two or more kinds of polymeric substances having different release properties selected from the group consisting of hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, carboxymethylethyl cellulose, methyl methacrylate-methacrylic acid copolymer, methacrylic acid-ethyl acrylate copolymer, methacrylic acid-methyl acrylate-methyl methacrylate copolymer, hydroxypropyl cellulose acetate succinate, polyvinyl acetate phthalate and shellac; said polymeric substance is soluble in the pH range of 6.0 to 7.5, and

(ii) a tablet, granule or fine granule comprising a core particle containing an active ingredient and enteric coat which is

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dissolved, thereby an active ingredient being released in the pH range of no less than 5.0, nor more than 6.0;

(42) The capsule according to the above-mentioned (41), wherein the pH-dependently soluble release-controlled coating-layer is formed on an intermediate layer which is formed on the core particle containing an active ingredient;

(43) The capsule according to the above-mentioned (41), wherein the active ingredient is lansoprazole;

(44) The capsule according to the above-mentioned (41), wherein the active ingredient is an optically active R-isomer of lansoprazole;

(45) The capsule according to the above-mentioned (41), wherein the active ingredient is an optically active S-isomer of lansoprazole;

(46) The capsule according to the above-mentioned (41), wherein the core particle containing an active ingredient contains a stabilizer of basic inorganic salt;

(47) The capsule according to the above-mentioned (41), wherein the pH-dependently soluble release-controlled coating-layer of the tablet, granule or fine granule in which the release of an active ingredient is controlled is a layer soluble in the pH range of no less than 6.5, nor more than 7.0;

(48) The capsule according to the above-mentioned (47), wherein the pH-dependently soluble release-controlled coating-layer contains a mixture of two or more kinds of methyl methacrylate-methacrylic acid copolymers having different release properties; and

(49) The capsule according to the above-mentioned (41), which further contains a gel-forming polymer.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a pharmaceutical composition containing a tablet, granule or fine granule, wherein the release of active ingredients is controlled, or a pharmaceutical composition containing these tablet, granule or fine granule and a gel-forming polymer, which delays digestive tract migration speed. The pharmaceutical composition of the present invention may be these tablet, granule or fine granule itself, or a form of a mixture of a tablet, granule or fine granule and a gel-forming polymer, or a capsule form in which the pharmaceutical composition is filled, but the capsule form is preferred in particular. It has been cleared that the persistence of blood levels after oral administration is remarkably prolonged by these combinations.

The release control of active ingredient in "a tablet, granule or fine granule wherein the release of active ingredient is controlled" of the present invention is performed by coating the active ingredient in a tablet, granule or fine granule with a layer controlling the release of active ingredient, or by dispersing the active ingredient in release-controlled matrices. Further, the "tablet, granule or fine granule wherein the release of active ingredient is controlled" of the present invention include also a tablet, granule or fine granule which is coated with a usual enteric coat which is dissolved at a pH of about 5.5, and tablets containing these granules or fine granules.

On the other hand, when the "release-controlled coating-layer" is mentioned in the present specification, it indicates a coating-layer having a function of further delaying or extending the release of active ingredient, such as a pH-dependently soluble layer which is dissolved at a higher pH region than a usual enteric coating which is dissolved at a pH of about 5.5, and a diffusion-controlled layer whose layer itself is not dissolved and which releases an active ingredient through pores which are formed in the layer. It does not include a usual enteric coat and layer which is dissolved at a pH of about 5.5,



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rapidly dissolved in the intestinal juice and release an active ingredient. Further, the pH mentioned here means a pH of the McIlvaine solution or Clark-Lubs solution. Hereinafter, the pH of a pH-dependently soluble layer means the pH of these solutions.

The coating-layer of the "release-controlled coating-layer" includes coating layers in a film form and those having larger thickness. Also, the coating-layer includes not only a coating-layer which entirely coats the inner core or layer but also the coating layers in which a part of the inner core or layer is not covered but most of the inner core or layer is coated (coating-layer which covers at least about 80% or more of the surface of the inner core or layer, and preferably covers the surface entirely).

The absorption from the digestive tract of the active ingredient from the pharmaceutical composition of the present invention is controlled by two kind of systems utilizing (1) a release control of active ingredient by a controlled release tablet, granule or fine granule and (2) retentive prolongation in the digestive tract of a tablet, granule or fine granule by a gel-forming polymer, or their combinations. Among the pharmaceutical composition of the present invention, the composition containing a gel-forming polymer forms adhesive gels by rapidly absorbing water by the gel-forming polymer in the digestive tract when orally administrated, and the tablet, granule or fine granule is retained on the surface of gels or in the gels to be gradually migrated through the digestive tract. The release of active ingredient is controlled in the meanwhile, the active ingredient is released continuously or in a pulsatile manner from the tablet, granule or fine granule by a controlled system, and as a result, the incidences of prolonged absorption and drug efficacy are attained.

The above-mentioned system enabling the persistence of therapeutic effective levels by controlling the release over a long time has advantages of therapeutic effectiveness at a low dose and reduction of side effects caused by initial rise of blood level and the like, as well as the reduction of administration times.

The gel-forming polymer may be a polymer which rapidly forms highly viscous gels by contacting with water and prolongs the retention time in the digestive tract. Such gel-forming polymer is preferably a polymer having a viscosity of about 3000 mPa·s or more for 5% aqueous solution at 25° C. Further, the gel-forming polymer is preferably a polymer usually having a molecular weight of about 400000 to 1000000 in general. As the gel-forming polymer, powder, granular or fine granular polymer is preferable for producing formulations. The gel-forming polymer includes a polyethylene oxide (PEO, for example, Polyox WSR 303 (molecular weight: 700000), Polyox WSR Coagulant (molecular weight: 500000), Polyox WSR 301 (molecular weight: 400000), Polyox WSR N-60K (molecular weight: 200000), and Polyox WSR 205 (molecular weight: 600000); manufactured by Dow Chemical Co., Ltd.), hydroxypropyl methylcellulose (HPMC, Metlose 90SH10000, Metlose 90SH50000, and Metlose 90SH30000; manufactured by Shin-Etsu Chemical Co., Ltd.), carboxymethylcellulose (CMC-Na, Sanlose F-1000MC), hydroxypropyl cellulose (HPC, for example, HPC-H, manufactured by Nippon Soda Co., Ltd.), hydroxyethyl cellulose (HEC), carboxyvinyl polymer (HIVISWAKO (R) 103, 104 and 105 manufactured by Wako Pure Chemical Industries Ltd.; CARBOPOL 943 manufactured by Goodrich Co., Ltd.), chitosan, sodium alginate, pectin and the like. These may be used alone or as a mixture of at least 2 or more of powders by mixing at an appropriate proportion. In particular, PEO, HPMC, HPC,

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CMC-Na, carboxyvinyl polymer and the like are preferably used as a gel-forming polymer.

One preferable form of a tablet, granule or fine granule wherein the release of active ingredient is controlled includes a tablet, granule or fine granule wherein a core particle containing at least one active ingredient is coated with a release-controlled coating-layer and a tablet containing these granules or fine granules. In order to prepare such core-possessing tablet, granule or fine granule, as a core particle can be used the tablet, granule or fine granule wherein an active ingredient is coated on a core which is an inactive carrier such as NON-PAREIL (NONPAREIL-101 (particle diameter: 850-710, 710-500, and 500-355), NONPAREIL-103 (particle diameter: 850-710, 710-500, and 500-355), NONPAREIL-105 (particle diameter: 710-500, 500-355 and 300-180); manufactured by Freund Industrial Co., Ltd.) and Celphere (CP-507 (particle diameter: 500-710), and CP-305 (particle diameter: 300-500); manufactured by Asahi Kasei Corporation); or the tablet prepared by using these granules or fine granules; or the particle obtained by granulation using an active ingredient and an excipient usually used for formulation. For example, they can be produced by the method disclosed in JP-A 63-301816. For example, when a core particle is prepared by coating an active ingredient on a core of an inactive carrier, core particles containing an active ingredient can be produced by wet granulation, using, for example, a centrifugal fluid-bed granulator (CF-mini, CF-360, manufactured by Freund Industrial Co., Ltd.) or a centrifugal fluidized coating granulator (POWREX MP-10), or the like. Further, coating may be carried out by dusting an active ingredient while adding a solution containing a binder and the like on the core of an inactive carrier with spray and the like. The production apparatuses are not limited and for example, it is preferable in the latter coating to produce them using a centrifugal fluid-bed granulator and the like. An active ingredient may be coated at two steps by carrying out the coating using the above-mentioned two apparatuses in combination. When an inactive carrier core is not used, a core particle can be produced by granulating excipient such as lactose, white sugar, mannitol, corn starch and crystalline cellulose and an active ingredient, using binders such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, a polyvinyl alcohol, Macrogol, Pulltronic F68, gum arabic, gelatin and starch, if necessary, adding disintegrants such as sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium cross carboxymethyl cellulose (Ac-Di-Sol, manufactured by FMC International Co., Ltd.), polyvinyl pyrrolidone and low substituted hydroxypropyl cellulose, with a stirring granulator, a wet extruding granulator, a fluidized bed granulator and the like.

Particles having desired sizes can be obtained by sieving the granules or fine granules obtained. The core particle may be prepared by dry granulation with a roller compactor and the like. Particles having a particle size of 50  $\mu$ m to 5 mm, preferably 100  $\mu$ m to 3 mm and more preferably 100  $\mu$ m to 2 mm are used.

The active ingredient-containing core particle thus obtained may be further coated to provide an intermediate coating layer, and the particle may be used as a core particle. It is preferable from the viewpoint of improving the stability of drugs that the intermediate coating layer is provided to intercept the direct contact of active ingredient-containing core particle with the release-controlled coating-layer when the active ingredient is an unstable drug against an acid, such as PPI and the like, etc. The intermediate coating layer may be formed by a plural number of layers.

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The coating materials for the intermediate coating layer include those obtained by appropriately compounding polymeric materials such as low substituted hydroxypropyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose (for example, TC-5 and the like), polyvinylpyrrolidone, polyvinyl alcohol, methylcellulose and hydroxyethyl methylcellulose with saccharides such as sucrose [purified sucrose (pulverized (powdered sugar), not pulverized) and the like], starch saccharide such as corn starch, lactose, sugar alcohol (D-mannitol, erythritol and the like). Excipients (for example, masking agents (titanium oxide and the like) and antistatic agents (titanium oxide, talc and the like) may be suitably added to the intermediate coating layer for the preparations mentioned below, if necessary.

The coating amount of the intermediate coating layer is usually about 0.02 part by weight to about 1.5 parts by weight based on 1 part by weight of granules containing an active ingredient, and preferably about 0.05 part by weight to about 1 part by weight. The coating can be carried out by conventional methods. For example, preferably, the components of the intermediate coating layer are diluted with purified water and sprayed to coat in liquid form. Then, it is preferable to carry out the coating while spraying a binder such as hydroxypropyl cellulose.

As the controlled release tablet, granule or fine granule contained in the pharmaceutical composition of the present invention, it is preferable to coat the above-mentioned core particle with a coating material which is pH-dependently dissolved/eluted to control the release, and to prepare the tablet, granule or fine granule having a release-controlled coating-layer, or the tablet containing these controlled release granules or fine granules. Herein, the "pH-dependently" means that the coating material is dissolved/eluted under the circumstances of more than a certain pH value to release an active ingredient. A usual enteric coat is eluted at a pH of about 5.5 to initiate the release of drug, while the coating material of the present invention is preferably a substance which is dissolved at a higher pH (preferably a pH of 6.0 or above and 7.5 or below, and more preferably a pH of 6.5 or above and below 7.2) and controls more favorably the release of drug in the stomach.

As a coating material for controlling pH-dependently the release of medical active ingredient, polymers such as hydroxypropyl methylcellulose phthalate (HP-55, HP-50 manufactured by Shin-Etsu Chemical Co., Ltd.), cellulose acetate phthalate, carboxymethyl ethylcellulose (CMEC manufactured by Freund Industrial Co., Ltd.), methyl methacrylate-methacrylic acid copolymer (Eudragit L100 (methacrylic acid copolymer L) or Eudragit S100 (methacrylic acid copolymer S); manufactured by Rohm Co.), methacrylic acid-ethyl acrylate copolymer (Eudragit L100-55 (dried methacrylic acid copolymer LD) or Eudragit L30D-55 (methacrylic acid copolymer LD); manufactured by Rohm Co.), methacrylic acid-methyl acrylate-methyl methacrylate copolymer (Eudragit FS30D manufactured by Rohm Co.), hydroxypropyl cellulose acetate succinate (HPMCAS manufactured by Shin-Etsu Chemical Co., Ltd.), polyvinyl acetate phthalate and shellac are used. The tablet, granule or fine granule may be those having two or more kinds of release-controlled coating-layers which have different release properties of active ingredient. The polymer as the above-mentioned coating material may be used alone or at least 2 or more kinds of the polymers may be used to coat in combination, or at least 2 or more kinds of the polymers may be coated sequentially to prepare multi-layers. It is desirable that the coating material is used alone or, if necessary, in combination so that the polymer is dissolved preferably at a pH of 6.0 or

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above, more preferably at a pH of 6.5 or above, and further more preferably at a pH of 6.75 or above. Further, more desirably, a polymer soluble at a pH of 6.0 or above and a polymer soluble at a pH of 7.0 or above are used in combination, and furthermore desirably, a polymer soluble at a pH of 6.0 or above and a polymer soluble at a pH of 7.0 or above are used in combination at a ratio of 1:0.5 to 1:5.

Further, plasticizers such as a polyethylene glycol, dibutyl sebacate, diethyl phthalate, triacetin and triethyl citrate, stabilizers and the like may be used for coating, if necessary. The amount of coating material is 5% to 200% based on the core particle, preferably 20% to 100% and more preferably 30% to 60%. The rate of elution of active ingredient from the active ingredient release-controlled tablet, granule or fine granule thus obtained is desirably 10% or less for 5 hours in a solution of pH 6.0, and 5% or less for one hour and 60% or more for 8 hours in a solution of pH 6.8.

The controlled release tablet, granule or fine granule (hereinafter, sometimes referred to simply as a controlled release granule) may be a tablet, granule or fine granule wherein a material which becomes viscous by contact with water, such as polyethylene oxide (PEO, for example, Polyox WSR 303 (molecular weight: 7000000), Polyox WSR Coagulant (molecular weight: 5000000), Polyox WSR 301 (molecular weight: 4000000), Polyox WSR N-60K (molecular weight: 2000000), and Polyox WSR 205 (molecular weight: 600000); manufactured by Dow Chemical Co., Ltd.), hydroxypropyl methylcellulose (HPMC, Metlose 90SH10000, Metlose 90SH50000, Metlose 90SH30000; manufactured by Shin-Etsu Chemical Co., Ltd.), carboxymethyl cellulose (CMC-Na, Sanlose F-1000MC), hydroxypropyl cellulose (HPC, for example, HPC-H manufactured by Nippon Soda Co., Ltd.), hydroxyethyl cellulose (HEC), carboxyvinyl polymer (HIVISWAKO (R) 103, 104, 105; manufactured by Wako Pure Chemical Industries Ltd.; CARBOPOL 943 manufactured by Goodrich Co., Ltd.), chitosan, sodium alginate and pectin, is coated on the active ingredient release-controlled tablet, granule or fine granule thus obtained.

The controlled release granule may be a form in which the core particle containing an active ingredient is coated with a diffusion-controlled layer having an action of controlling the release of active ingredient by diffusion. The materials for these diffusion-controlled layer include ethyl acrylate-methyl methacrylate-trimethylammoniumethyl methacrylate chloride copolymer (Eudragit RS (aminoalkyl methacrylate copolymer RS) or Eudragit RL (aminoalkyl methacrylate copolymer RL); manufactured by Rohm Co.), methyl methacrylate-ethyl acrylate copolymer (Eudragit NE30D manufactured by Rohm Co.), ethyl cellulose and the like. Further, these materials for layer may be mixed at an appropriate ratio, and can be used by mixing with hydrophilic pore forming substances such as HPMC, HPC, carboxyvinyl polymer, polyethylene glycol 6000, lactose, mannitol and organic acid at a fixed ratio.

Further, in order to prepare the tablet, granule or fine granule wherein the release of active ingredient is controlled to initiate after a fixed lag time, a disintegrant layer is provided between the core particle containing an active ingredient and the release-controlled coating-layer by coating a swelling substance such as a disintegrant previously before coating the above-mentioned diffusion-controlled layer. For example, preferably, a swelling substance such as cross carmellose sodium (Ac-Di-Sol, manufactured by FMC International Co.), carmellose calcium (ECG 505, manufactured by Gotoku Chemicals Co.), CROSSPOVIDON (ISP Inc.) and low substituted hydroxypropyl cellulose (L-HPC manufactured by Shin-Etsu Chemical Co., Ltd.) is primarily coated on a core



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particle, and then the resulting coated particle is secondarily coated with a diffusion-controlled layer which is prepared by mixing at a fixed ratio one or more kinds of polymers selected from ethyl methacrylate-methyl methacrylate-trimethylammonium-methyl methacrylate chloride copolymer (Eudragit RS or Eudragit RL; manufactured by Rohm Co.), methyl methacrylate-ethyl acrylate copolymer (Eudragit NE30D manufactured by Rohm Co.), ethyl cellulose and the like; with hydrophilic pore forming substances such as HPMC, HPC, carboxyvinyl polymer, polyethylene glycol 6000, lactose, mannitol and an organic acid. The secondary coating material may be enteric polymers which release pH-dependently an active ingredient, such as hydroxypropyl methylcellulose phthalate (HP-55, HP-50; manufactured by Shin-Etsu Chemical Co., Ltd.), cellulose acetate phthalate, carboxymethyl ethylcellulose (CMC; manufactured by Freund Industrial Co., Ltd.), methyl methacrylate-methacrylic acid copolymer (Eudragit L100 (methacrylic acid copolymer L) or Eudragit S100 (methacrylic acid copolymer S); manufactured by Rohm Co.), methacrylic acid-ethyl acrylate copolymer (Eudragit L100-55 (dried methacrylic acid copolymer LD) or Eudragit L30D-55 (methacrylic acid copolymer LD); manufactured by Rohm Co.), methacrylic acid-methyl acrylate-methyl methacrylate copolymer (Eudragit FS30D; manufactured by Rohm Co.), hydroxypropyl cellulose acetate succinate (HPMCAS; manufactured by Shin-Etsu Chemical Co., Ltd.), polyvinyl acetate and shellac. The amount of coating material is 1% to 200% based on the core particle, preferably 20% to 100% and more preferably 30% to 60%.

Plasticizers such as polyethylene glycol, dibutyl sebacate, diethyl phthalate, triacetin and triethyl citrate, stabilizers and the like may be used for coating, if necessary. The controlled release tablet, granule or fine granule may be a tablet, granule or fine granule wherein a material which becomes viscous by contact with water, such as polyethylene oxide (PEO, for example, Polyox WSR 303 (molecular weight: 7000000), Polyox WSR Coagulant (molecular weight: 5000000), Polyox WSR 301 (molecular weight: 4000000), Polyox WSR N-60K (molecular weight: 2000000), and Polyox WSR 205 (molecular weight: 600000); manufactured by Dow Chemical Co., Ltd.), hydroxypropyl methylcellulose (HPMC, Metlose 90SH10000, Metlose 90SH50000, Metlose 90SH30000; manufactured by Shin-Etsu Chemical Co., Ltd.), carboxymethyl cellulose (CMC-Na, Sanlose F-1000MC), hydroxypropyl cellulose (HPC, for example, HPC-H manufactured by Nippon Soda Co., Ltd.), hydroxyethyl cellulose (HEC), carboxyvinyl polymer (HIVISWAKO (R) 103, 104, 105; manufactured by Wako Pure Chemical Industries Ltd.; CARBOPOL 943 manufactured by Goodrich Co., Ltd.), chitosan, sodium alginate and pectin, is coated on the active ingredient release-controlled tablet, granule or fine granule thus obtained.

In the tablet, granule or fine granule having 2 or more kinds of release-controlled coating-layers having different release properties of active ingredient, a layer containing an active ingredient may be set up between said release-controlled coating-layers. A form of these multi-layer structure containing an active ingredient between release-controlled coating-layers includes a tablet, granule or fine granule which is prepared by coating an active ingredient on the tablet, granule or fine granule wherein the release of active ingredient is controlled by the release-controlled coating-layer of the present invention, followed by further coating with the release-controlled coating-layer of the present invention.

Another form of the tablet, granule or fine granule wherein the release of at least one of the active ingredients is con-

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trolled may be a tablet, granule or fine granule in which the active ingredients are dispersed in a release-controlled matrix. These controlled release tablet, granule or fine granule can be produced by homogeneously dispersing the active ingredients into hydrophobic carriers such as waxes such as hardened castor oil, hardened rape seed oil, stearic acid and stearyl alcohol, and polyglycerin fatty acid ester. The matrix is a composition in which the active ingredients are homogeneously dispersed in a carrier. If necessary, excipients such as lactose, mannitol, corn starch and crystalline cellulose which are usually used for preparation of a drug may be dispersed with the active ingredients. Further, powders of polyoxyethylene oxide, cross-linked acrylic acid polymer (HIVISWAKO (R) 103, 104 and 105, CARBOPOL), HPMC, HPC, chitosan and the like which form viscous gels by contact with water may be dispersed into the matrix together with the active ingredients and excipients.

As the preparation method, they can be prepared by methods such as spray dry, spray chilling and melt granulation.

The controlled release tablet, granule or fine granule may be a tablet, granule or fine granule wherein a material which becomes viscous by contact with water, such as polyethylene oxide (PEO, for example, Polyox WSR 303 (molecular weight: 7000000), Polyox WSR Coagulant (molecular weight: 5000000), Polyox WSR 301 (molecular weight: 4000000), Polyox WSR N-60K (molecular weight: 2000000), and Polyox WSR 205 (molecular weight: 600000); manufactured by Dow Chemical Co., Ltd.), hydroxypropyl methylcellulose (HPMC, Metlose 90SH10000, Metlose 90SH50000, Metlose 90SH30000; manufactured by Shin-Etsu Chemical Co., Ltd.), carboxymethyl cellulose (CMC-Na, Sanlose F-1000MC), hydroxypropyl cellulose (HPC, for example, HPC-H manufactured by Nippon Soda Co., Ltd.), hydroxyethyl cellulose (HEC), carboxyvinyl polymer (HIVISWAKO (R) 103, 104, 105; manufactured by Wako Pure Chemical Industries Ltd.; CARBOPOL 943 manufactured by Goodrich Co., Ltd.), chitosan, sodium alginate and pectin, is coated on the active ingredient release-controlled tablet, granule or fine granule thus obtained. These materials which become viscous by contact with water may be coexisted in one preparation such as a capsule and the like as well as using for coat.

The tablet, granule or fine granule of the present invention wherein the release of active ingredient is controlled may be a form having the above-mentioned various kinds of release-controlled coating-layers, release-controlled matrixes and the like in combination.

As the size of tablet, granule or fine granule wherein the release of active ingredient is controlled, particles having a particle size of 50  $\mu$ m to 5 mm, preferably 100  $\mu$ m to 3 mm and more preferably 100  $\mu$ m to 2 mm are used. Granules or fine granules having a particle size of about 100  $\mu$ m to 1500  $\mu$ m are most preferred.

Further, additives such as excipients for providing preparations (for example, glucose, fructose, lactose, sucrose, D-mannitol, erythritol, multitol, trehalose, sorbitol, corn starch, potato starch, wheat starch, rice starch, crystalline cellulose, silicic acid anhydride, calcium metaphosphate, sedimented calcium carbonate, calcium silicate, and the like), binders (for example, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, methyl cellulose, polyvinyl alcohol, carboxymethyl cellulose sodium, partial  $\alpha$  starch,  $\alpha$  starch, sodium alginate, pullulan, gum arabic powder, gelatin and the like), disintegrants (for example, low substituted hydroxypropyl cellulose, carmellose, carmellose calcium, carboxymethylstarch sodium, cross carmellose sodium, crosspovidon, hydroxypropylstarch and the like),

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flavoring agents (for example, citric acid, ascorbic acid, tartaric acid, malic acid, aspartame, acesulfam potassium, thaumatin, saccharin sodium, glycyrrhizin dipotassium, sodium glutamate, sodium 5'-inosinate, sodium 5'-guanylate and the like), surfactants (for example, polysolvate (polysolvate 80 and the like), polyoxyethylene-polyoxypropylene copolymer, sodium laurylsulfate and the like), perfumes (for example, lemon oil, orange oil, menthol, peppermint oil and the like), lubricants (for example, magnesium stearate, sucrose fatty acid ester, sodium stearyl fumarate, stearic acid, talc, polyethylene glycol and the like), colorants (for example, titanium oxide, edible Yellow No.5, edible Blue No.2, iron (III) oxide, yellow iron (III) oxide, and the like), antioxidants (for example, sodium ascorbate, L-cysteine, sodium bisulfate, and the like), masking agents (for example, titanium oxide and the like), and antistatic agents (for example, talc, titanium oxide and the like) can be used.

The particle diameter of raw materials used here are not particularly limited, and particles having a diameter of about 500  $\mu\text{m}$  or less are preferred from the viewpoint of productivity and dosing.

The tablet, granule or fine granule thus obtained may be administrated as it is by mixing with a digestive tract retentive gel-forming polymer, or can be formulated as a capsule by filling in capsules. The amount of the gel-forming polymer being retentive in the digestive tract is 0.1% to 100% relative to the controlled release tablet, granule or fine granule, preferably 2% to 50%, more preferably 10% to 40%, and further more preferably 10% to 35%.

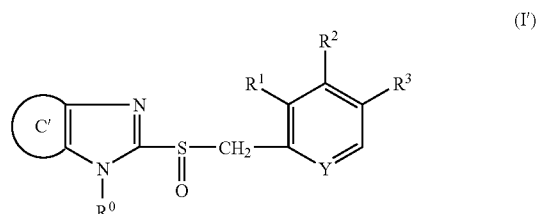
The pharmaceutical composition of the present invention thus obtained is a composition having an extended activity of drug by a release-controlled system wherein therapeutic effect is revealed for at least 6 hours, preferably 8 hours, more preferably 12 hours and further preferably 16 hours.

The active ingredients are not particularly limited, and can be applied irrespective of the region of drug efficacy. Exemplified are anti-inflammatory drugs such as indomethacin and acetaminophen, analgesics such as morphine, cardiovascular agonists such as diazepam and diltiazepam, antihistamines such as chlorophenylamine maleate, antitumors such as fluorouracil and aclarubicin, narcotics such as midazolam, antihemostasis agents such as ephedrine, diuretics such as hydrochlorothiazide and furosemide, bronchodilators such as theophylline, antitussives such as codeine, antiarrhythmic agents such as quinidine and dioxin, antidiabetics such as tolbutamide, pioglitazone and troglitazone, vitamins such as ascorbic acid, anticonvulsants such as phenitoin, local anesthetics such as lidocaine, adrenocortical hormones such as hydrocortisone, drugs effective for central nerve such as eisa, hypolipidemic drugs such as pravastatin, antibiotics such as amoxicillin and cephalixin, digestive tract exitomotory agents such as mosapride and cisapride, H<sub>2</sub> blockers such as famotidine, ranitidine and cimetidine which are the remedies of gastritis, symptomatic gastroesophageal reflux disease, and gastric and duodenal ulcers, and benzimidazole proton pump inhibitors (PPI) represented by lansoprazole and optically active isomers thereof (R-isomer and S-isomer, preferably R-isomer (hereinafter, occasionally referred to as Compound A)), omeprazole and optically active isomers thereof (S-isomer: S omeprazole), rabeprazole and optically active isomers thereof, pantoprazole and optically active isomers thereof and the like, and imidazopyridine PPI represented by tenatoprazole and the like.

According to the present invention, the preparations which contain, as an active ingredient, a PPI such as acid-labile imidazole compounds represented by the following general formula (I') such as lansoprazole and optically active isomers

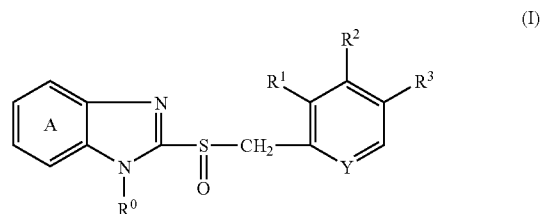
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thereof, in particular, acid-labile benzimidazole compounds represented by the following formula (I), and relatively acid-stable imidazole compound derivatives (prodrug type PPI) represented by the following general formula (II) or (III) or salts thereof or optically active isomers thereof have an excellent sustainability of drug efficacy. As a result, dosing compliance is also improved and therapeutic effect is increased.



Wherein ring C' indicates a benzene ring optionally having a substituent group or an aromatic monocyclic heterocyclic ring optionally having a substituent group; R<sup>0</sup> indicates a hydrogen atom, an aralkyl group optionally having a substituent group, an acyl group or an acyloxy group; R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are the same or different and indicate a hydrogen atom, an alkyl group optionally having a substituent group, an alkoxy group optionally having a substituent group or an amino group optionally having a substituent group, respectively; and Y indicates a nitrogen atom or CH.

Among the compounds represented by the above-mentioned formula (I'), the compound in which the ring C' is a benzene ring optionally having a substituent group is particularly represented by the following formula (I).



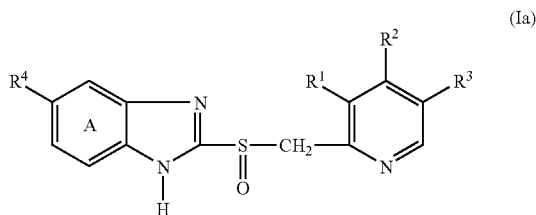
Namely, in the formula (I), ring A indicates a benzene ring optionally having a substituent group, and R<sup>0</sup>, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and Y have the same meaning as in the above-mentioned formula (I').

In the above-mentioned formula (I), the preferable compound is a compound wherein ring A is a benzene ring which may have a substituent group selected from a halogen atom, an optionally halogenated C<sub>1-4</sub> alkyl group, an optionally halogenated C<sub>1-4</sub> alkoxy group and a 5- or 6-membered heterocyclic group; R<sup>0</sup> is a hydrogen atom, an optionally substituted aralkyl group, an acyl group or an acyloxy group; R<sup>1</sup> is a C<sub>1-6</sub> alkyl group, a C<sub>1-6</sub> alkoxy group, a C<sub>1-6</sub> alkoxy-C<sub>1-6</sub> alkoxy group or a di-C<sub>1-6</sub> alkylamino group; R<sup>2</sup> is a hydrogen atom, a C<sub>1-6</sub> alkoxy-C<sub>1-6</sub> alkoxy group, or an optionally halogenated C<sub>1-6</sub> alkoxy group; R<sup>3</sup> is a hydrogen atom or a C<sub>1-6</sub> alkyl group, and Y is a nitrogen atom.

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In particular, the preferable compound is a compound represented by the formula (Ia);



wherein  $R^1$  indicates a  $C_{1-3}$  alkyl group or a  $C_{1-3}$  alkoxy group;  $R^2$  indicates a  $C_{1-3}$  alkoxy group which may be halogenated or may be substituted with a  $C_{1-3}$  alkoxy group;  $R^3$  indicates a hydrogen atom or a  $C_{1-3}$  alkyl group, and  $R^4$  indicates a hydrogen atom, an optionally halogenated  $C_{1-3}$  alkoxy group or a pyrrolyl group (for example, 1-, 2- or 3-pyrrolyl group).

In the formula (Ia), the compound wherein  $R^1$  is a  $C_{1-3}$  alkyl group;  $R^2$  is an optionally halogenated  $C_{1-3}$  alkoxy group;  $R^3$  is a hydrogen atom and  $R^4$  is a hydrogen atom or an optionally halogenated  $C_{1-3}$  alkoxy group is particularly preferred.

In the compound represented by the above-mentioned formula (I) (hereinafter, referred to as Compound (I)), the "substituent group" of the "benzene ring optionally having a substituent group" represented by ring A includes, for example, a halogen atom, a nitro group, an alkyl group optionally having a substituent group, a hydroxy group, an alkoxy group optionally having a substituent group, an aryl group, an aryloxy group, a carboxy group, an acyl group, an acyloxy group, a 5- to 10-membered heterocyclic group and the like. The benzene ring may be substituted with about 1 to 3 of these substituent groups. When the number of substituents is 2 or more, each substituent groups may be the same or different. Among these substituent groups, a halogen atom, an alkyl group optionally having a substituent group, an alkoxy group optionally having a substituent group and the like are preferred.

The halogen atom includes fluorine, chlorine, bromine atom and the like. Among these, fluorine is preferred.

As the "alkyl group" of the "alkyl group optionally having a substituent group", for example, a  $C_{1-7}$  alkyl group (for example, a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl group and the like) is exemplified. As the "substituent group" of the "alkyl group optionally having a substituent group", for example, a halogen atom, a hydroxy group, a  $C_{1-6}$  alkoxy group (for example, methoxy, ethoxy, propoxy, butoxy and the like), a  $C_{1-6}$  alkoxy-carbonyl group (for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and the like), a carbamoyl group and the like can be exemplified, and the number of these substituent groups may be about 1 to 3. When the number of substituent group is 2 or more, each substituent groups may be the same or different.

The "alkoxy group" of the "alkoxy group optionally having a substituent group" includes, for example, a  $C_{1-6}$  alkoxy group (for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy and the like) and the like. The "substituent group" of the "alkoxy group optionally having a substituent group" are exemplified by those for the above-mentioned "substituent group" of the "alkyl group optionally having a substituent group", and the number of the substituent group is the same.

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The "aryl group" include, for example, a  $C_{6-14}$  aryl group (for example, a phenyl, 1-naphthyl, 2-naphthyl, biphenyl, 2-anthryl group and the like) and the like.

The "aryloxy group" includes, for example, a  $C_{6-14}$  aryloxy group (for example, a phenyloxy, 1-naphthyloxy, 2-naphthyloxy and the like) and the like.

The "acyl group" includes, for example, a formyl, alkyl-carbonyl, alkoxy-carbonyl, carbamoyl, alkylcarbamoyl, alkylsulfinyl, alkylsulfonyl group and the like.

The "alkylcarbonyl group" includes, a  $C_{1-6}$  alkyl-carbonyl group (for example, acetyl, propionyl group and the like) and the like.

The "alkoxycarbonyl group" includes, for example, a  $C_{1-6}$  alkoxy-carbonyl group (for example, a methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl group and the like) and the like.

The "alkylcarbamoyl group" include, a  $N-C_{1-6}$  alkyl-carbamoyl group (for example, methylcarbamoyl, ethylcarbamoyl group and the like), a  $N,N$ -di- $C_{1-6}$  alkyl-carbamoyl group (for example,  $N,N$ -dimethylcarbamoyl,  $N,N$ -diethylcarbamoyl group and the like), and the like.

The "alkylsulfinyl group" includes, for example, a  $C_{1-7}$  alkylsulfinyl group (for example, a methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl group and the like) and the like.

The "alkylsulfonyl group" includes, for example, a  $C_{1-7}$  alkylsulfonyl group (for example, a methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl group and the like) and the like.

The "acyloxy group" includes, for example, an alkylcarbonyloxy group, an alkoxy-carbonyloxy group, a carbamoyloxy group, an alkylcarbamoyloxy group, an alkylsulfinyloxy group, an alkylsulfonyloxy group and the like.

The "alkylcarbonyloxy group" includes, a  $C_{1-6}$  alkyl-carbonyloxy group (for example, acetyloxy, propionyloxy group and the like) and the like.

The "alkoxycarbonyloxy group" includes, for example, a  $C_{1-6}$  alkoxy-carbonyloxy group (for example, methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy group and the like) and the like.

The "alkylcarbamoyloxy group" includes, a  $C_{1-6}$  alkylcarbamoyloxy group (for example, methylcarbamoyloxy, ethylcarbamoyloxy group and the like) and the like.

The "alkylsulfinyloxy group" includes, for example, a  $C_{1-7}$  alkylsulfinyloxy group (for example, methylsulfinyloxy, ethylsulfinyloxy, propylsulfinyloxy, isopropylsulfinyloxy group and the like) and the like.

The "alkylsulfonyloxy group" includes, for example, a  $C_{1-7}$  alkylsulfonyloxy group (for example, methylsulfonyloxy, ethylsulfonyloxy, propylsulfonyloxy, isopropylsulfonyloxy group and the like) and the like.

The 5- to 10-membered heterocyclic group include, for example, a 5- to 10-membered (preferably 5- or 6-membered) heterocyclic group which contains one or more (for example, one to three) hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to a carbon atom. Specific example includes 2- or 3-thienyl group, 2-, 3- or 4-pyridyl group, 2- or 3-furyl group, 1-, 2- or 3-pyrrolyl group, 2-, 3-, 4-, 5- or 8-quinolyl group, 1-, 3-, 4- or 5-isoquinolyl group, 1-, 2- or 3-indolyl group; Among these, 5- or 6-membered heterocyclic groups such as 1-, 2- or 3-pyrrolyl groups are preferred.

Ring A is preferably a benzene ring which may have 1 or 2 substituent groups selected from a halogen atom, an optionally halogenated  $C_{1-4}$  alkyl group, an optionally halogenated  $C_{1-4}$  alkoxy group and 5- or 6-membered heterocyclic group.



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In the above-mentioned formula (I'), the "aromatic monocyclic heterocyclic ring" of the "optionally substituted aromatic monocyclic heterocyclic ring" represented by ring C' includes, for example, 5- to 6-membered aromatic monocyclic heterocyclic rings such as furan, thiophene, pyrrole, oxazole, isoxazole, thiazole, isothiazole, imidazole, pyrazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, furazane, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine and triazine. As the "aromatic monocyclic heterocyclic ring" represented by ring C', "a benzene ring which may have a substituent group" represented by the above-mentioned ring A and "a pyridine ring optionally having a substituent group" are particularly preferred. The "pyridine ring optionally having a substituent group" represented by ring C' may have 1 to 4 of the same substituent groups as those exemplified with respect to the "benzene ring which may have a substituent group" represented by the above-mentioned ring A at substitutable positions.

The position wherein "aromatic monocyclic heterocyclic ring" of the "aromatic monocyclic heterocyclic ring optionally having a substituent group" is condensed with an imidazole moiety is not specifically limited.

In the above-mentioned formula (I') or (I), the "aralkyl group" of the "aralkyl group optionally having a substituent group" represented by R<sup>0</sup> includes, for example, a C<sub>7-16</sub> aralkyl group (for example, C<sub>6-10</sub> arylC<sub>1-6</sub> alkyl group such as benzyl and phenethyl and the like) and the like. Examples of the "substituent group" of the "aralkyl group optionally having a substituent group" include the same groups as those exemplified with respect to the "substituent group" of the above-mentioned "alkyl group optionally having a substituent group", and the number of the substituent groups is 1 to about 4. When the number of the substituent group is 2 or more, each substituent groups may be the same or different.

The "acyl group" represented by R<sup>0</sup> includes, for example, the "acyl group" described as the substituent group of the above-mentioned ring A.

The "acyloxy group" represented by R<sup>0</sup> includes, for example, the "acyloxy group" described as the substituent group of the above-mentioned ring A.

The preferable R<sup>0</sup> is a hydrogen atom.

In the above-mentioned formula (I') or (I), the "alkyl group optionally having a substituent group" represented by R<sup>1</sup>, R<sup>2</sup> or R<sup>3</sup> includes the "alkyl group optionally having a substituent group" described as the substituent group of the above-mentioned ring A.

The "alkoxy group optionally having a substituent group" represented by R<sup>1</sup>, R<sup>2</sup> or R<sup>3</sup> includes the "alkoxy group optionally having a substituent group" described as the substituent group of the above-mentioned ring A.

The "amino group optionally having a substituent group" represented by R<sup>1</sup>, R<sup>2</sup> or R<sup>3</sup> includes, for example, an amino group, a mono-C<sub>1-6</sub> alkylamino group (for example, methylamino, ethylamino and the like), a mono-C<sub>6-14</sub> arylamino group (for example, phenylamino, 1-naphthylamino, 2-naphthylamino and the like), a di-C<sub>1-6</sub> alkylamino group (for example, dimethylamino, diethylamino and the like), a di-C<sub>6-14</sub> arylamino group (for example, diphenylamino and the like) and the like.

The preferable R<sup>1</sup> is a C<sub>1-6</sub> alkyl group, a C<sub>1-6</sub> alkoxy group, a C<sub>1-6</sub> alkoxy-C<sub>1-6</sub> alkoxy group and a di-C<sub>1-6</sub> alkylamino group. Further preferable R<sup>2</sup> is a C<sub>1-3</sub> alkyl group or a C<sub>1-3</sub> alkoxy group.

The preferable R<sup>2</sup> is a hydrogen atom, a C<sub>1-6</sub> alkoxy-C<sub>1-6</sub> alkoxy group or an optionally halogenated C<sub>1-6</sub> alkoxy group.

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Further preferable R<sup>3</sup> is a C<sub>1-3</sub> alkoxy group which may be optionally halogenated or may be optionally substituted with a C<sub>1-3</sub> alkoxy group.

The preferable R<sup>3</sup> is a hydrogen atom or a C<sub>1-6</sub> alkyl group. Further preferable R<sup>3</sup> is a hydrogen atom or a C<sub>1-3</sub> alkyl group (in particular, a hydrogen atom).

The preferable Y is a nitrogen atom.

As the specific example of the compound (I), the following compounds are exemplified.

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (lansoprazole),  
2-[[[(3,5-dimethyl-4-methoxy-2-pyridinyl)methyl]sulfinyl]-5-methoxy-1H-benzimidazole,  
2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole sodium salt,  
5-difluoromethoxy-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and the like.

Among these compounds, lansoprazole, namely 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole is preferable in particular.

The present invention is preferably applied to the PPI of imidazopyridine compound in addition to the PPI of the above-mentioned benzimidazole compound. As the PPI of the imidazopyridine compound, for example, tenatoprazole is exemplified.

Further, the above-mentioned compound (I) and compound (I') including the imidazopyridine compound may be racemic, and optically active compounds such as R-isomer and S-isomer. For example, the optically active compounds such as optically active compound of lansoprazole, that is, (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole and (S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole are preferable for the present invention in particular. Further, for lansoprazole, lansoprazole R-isomer and lansoprazole S-isomer, crystals are usually preferred, but since they are stabilized by preparation itself as described later and stabilized by compounding a basic inorganic salt and further providing an intermediate layer, those being amorphous as well as crystalline can be also used.

The salt of compound (I') and compound (I) is preferably a pharmacologically acceptable salt, and for example, a salt with an inorganic base, a salt with an organic base, a salt with a basic amino acid and the like are mentioned.

The preferable salt with an inorganic base includes, for example, alkali metal salts such as sodium salt and potassium salt; alkali earth metal salts such as calcium salt and magnesium salt; ammonium salt and the like.

The preferable example of the salt with an organic base includes, for example, salts with an alkylamine (trimethylamine, triethylamine and the like), a heterocyclic amine (pyridine, picoline and the like), an alkanolamine (ethanolamine, diethanolamine, triethanolamine and the like), dicyclohexylamine, N,N'-dibenzylethylenediamine and the like.

The preferable example of the salt with a basic amino acid includes, for example, salts with arginine, lysine, ornithine and the like.

Among these salts, an alkali metal salt and an alkali earth metal salt are preferred. A sodium salt is preferred particularly.

The compound (I') or (I) can be produced by known methods, and are produced by methods disclosed in, for example, JP-A 61-50978, U.S. Pat. No. 4,628,098, JP-A 10-195068, WO 98/21201, JP-A 52-62275, JP-A 54-141783 and the like, or analogous methods thereto. Further, the optically active compound (I) can be obtained by optical resolution methods (a fractional recrystallization method, a chiral column

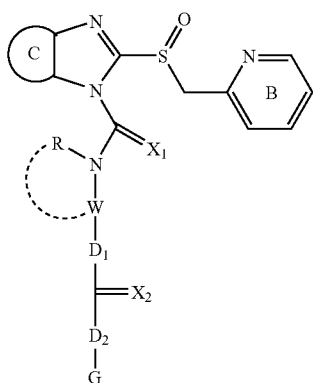
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method, a diastereomer method, a method using microorganism or enzyme, and the like) and an asymmetric oxidation method, etc. Further, lansoprazole R-isomer can be produced according to production methods described in, for example, WO 00-78745, WO 01/83473 and the like.

The benzimidazole compound having antitumor activity used in the present invention is preferably lansoprazole, omeprazole, rabeprazole, pantoprazole, leminoprazole, tenatoprazole (TU-199) and the like, or optically active compounds thereof and pharmacologically acceptable salts thereof. Lansoprazole or an optically active compound thereof, in particular R-isomer is preferred. Lansoprazole or an optically active compound thereof, in particular R-isomer is preferably in a form of crystal, but may be an amorphous form. Further, they are also suitably applied to the prodrug of these PPIs.

Examples of these preferable prodrugs include the compound represented by the following general formula (II) and (III) in addition to the prodrug which is included in compound (I) or (I').



In the compound represented by the above formula (II) (hereinafter, referred to as compound (II)), ring B designates a "pyridine ring optionally having substituents".

The pyridine ring of the "pyridine ring optionally having substituents" represented by ring B may have 1 to 4 substituents at substitutable positions thereof. As the substituent, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine etc.), a hydrocarbon group optionally having substituents (e.g., alkyl group having 1 to 6 carbon atoms such as methyl group, ethyl group, n-propyl group etc., and the like), an amino group optionally having substituents (e.g., amino; amino group mono- or di-substituted by alkyl group having 1 to 6 carbon atoms, such as methylamino, dimethylamino, ethylamino, diethylamino group etc., and the like), an amide group (e.g., C<sub>1-3</sub> acylamino group such as formamide, acetamide etc., and the like), a lower alkoxy group optionally having substituents (e.g., alkoxy group having 1 to 6 carbon atoms such as methoxy, ethoxy, 2,2,2-trifluoroethoxy, 3-methoxypropoxy group and the like), a lower alkylenedioxy group (e.g., C<sub>1-3</sub> alkylenedioxy group such as methylenedioxy, ethylenedioxy etc., and the like) and the like can be mentioned.

As the substituent, which is the substituent of the "pyridine ring optionally having substituents" represented by ring B can have, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine etc.), a lower alkyl group (e.g., alkyl group having 1 to 6 carbon atoms such as methyl, ethyl, propyl group and the like), a lower alkenyl group (e.g., alkenyl group having 2 to 6 carbon atoms such as vinyl, allyl

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group and the like), a lower alkynyl group (e.g., alkynyl group having 2 to 6 carbon atoms such as ethynyl, propargyl group and the like), a cycloalkyl group (e.g., cycloalkyl group having 3 to 8 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl group and the like), a lower alkoxy group (e.g., alkoxy group having 1 to 6 carbon atoms such as methoxy, ethoxy group and the like), a nitro group, a cyano group, a hydroxy group, a thiol group, a carboxyl group, a lower alkanoyl group (e.g., formyl; C<sub>1</sub>-C<sub>6</sub> alkyl-carbonyl group, such as acetyl, propionyl, butyryl group and the like), a lower alkanoyloxy group (e.g., formyloxy; C<sub>1</sub>-C<sub>6</sub> alkyl-carbonyloxy group, such as acetyloxy, propionyloxy group and the like), a lower alkoxy-carbonyl group (e.g., C<sub>1</sub>-C<sub>6</sub> alkoxy-carbonyl group, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl group and the like), an aralkyloxy-carbonyl group (e.g., C<sub>7</sub>-C<sub>11</sub> aralkyloxy-carbonyl group, such as benzoyloxy-carbonyl group and the like), an aryl group (e.g., aryl group having 6 to 14 carbon atoms such as phenyl, naphthyl group and the like), an aryloxy group (e.g., aryloxy group having 6 to 14 carbon atoms such as phenyloxy, naphthyloxy group and the like), an arylcarbonyl group (e.g., C<sub>6</sub>-C<sub>14</sub> aryl-carbonyl group, such as benzoyl, naphthoyl group and the like), an arylcarbonyloxy group (e.g., C<sub>6</sub>-C<sub>14</sub> aryl-carbonyloxy group, such as benzoyloxy, naphthoyloxy group and the like), a carbamoyl group optionally having substituents (e.g., carbamoyl; carbamoyl group mono- or di-substituted by alkyl group having 1 to 6 carbon atoms, such as methylcarbamoyl, dimethylcarbamoyl group etc., and the like), an amino group optionally having substituents (e.g., amino; amino group mono- or di-substituted by alkyl group having 1 to 6 carbon atoms, such as methylamino, dimethylamino, ethylamino, diethylamino group etc., and the like), and the like, can be mentioned, wherein the number of substituents and the position of the substitution are not particularly limited.

While the number of substituents and the position of substitution of the "pyridine ring optionally having substituents" represented by ring B are not particularly limited, 1 to 3 substituents mentioned above preferably substitute any of the 3-, 4- and 5-positions of the pyridine ring.

As the "pyridine ring optionally having substituents" represented by ring B, 3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl is preferable.

In the present invention, ring C represents a "benzene ring optionally having substituents" or an "aromatic monocyclic heterocycle optionally having substituents", which is condensed with an imidazole part. Of these, the former is preferable.

The benzene ring of the "benzene ring optionally having substituents" represented by ring C may have 1 to 4 substituents at substitutable positions thereof. As the substituent, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine etc.), a hydrocarbon group optionally having substituents (e.g., alkyl group having 1 to 6 carbon atoms selected from methyl group, ethyl group, n-propyl group etc., and the like), an amino group optionally having substituents (e.g., amino; amino group mono- or di-substituted by alkyl group having 1 to 6 carbon atoms, such as methylamino, dimethylamino, ethylamino, diethylamino group etc., and the like), an amide group (e.g., C<sub>1-3</sub> acylamino group such as formamide, acetamide etc., and the like), a lower alkoxy group optionally having substituents (e.g., alkoxy group having 1 to 6 carbon atoms, such as methoxy, ethoxy, difluoromethoxy group etc., and the like), a lower alkylenedioxy group (e.g., C<sub>1-3</sub> alkylenedioxy group such as methylenedioxy, ethylenedioxy etc., and the like), and the like can be mentioned.



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As the substituent, which is the substituent of the "benzene ring optionally having substituents" represented by ring C can have, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine etc.), a lower alkyl group (e.g., alkyl group having 1 to 6 carbon atoms such as methyl, ethyl, propyl group and the like), a lower alkenyl group (e.g., alkenyl group having 2 to 6 carbon atoms such as vinyl, allyl group and the like), a lower alkynyl group (e.g., alkynyl group having 2 to 6 carbon atoms such as ethynyl, propargyl group and the like), a cycloalkyl group (e.g., cycloalkyl group having 3 to 8 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl group and the like), a lower alkoxy group (e.g., alkoxy group having 1 to 6 carbon atoms such as methoxy, ethoxy group and the like), a nitro group, a cyano group, a hydroxy group, a thiol group, a carboxyl group, a lower alkanoyl group (e.g., formyl; C<sub>1-6</sub> alkyl-carbonyl group, such as acetyl, propionyl, butyryl group and the like), a lower alkanoyloxy group (e.g., formyloxy; C<sub>1-6</sub> alkyl-carbonyloxy group, such as acetyloxy, propionyloxy group and the like), a lower alkoxy carbonyl group (e.g., C<sub>1-6</sub> alkoxy-carbonyl group, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl group and the like), an aralkyloxycarbonyl group (e.g., C<sub>7-17</sub> aralkyloxy-carbonyl group, such as benzyloxycarbonyl group and the like), an aryl group (e.g., aryl group having 6 to 14 carbon atoms such as phenyl, naphthyl group and the like), an aryloxy group (e.g., aryloxy group having 6 to 14 carbon atoms such as phenyloxy, naphthyloxy group and the like), an arylcarbonyl group (e.g., C<sub>6-14</sub> aryl-carbonyl group, such as benzoyl, naphthoyl group and the like), an arylcarbonyloxy group (e.g., C<sub>6-14</sub> aryl-carbonyloxy group, such as benzoyloxy, naphthoyloxy group and the like), a carbamoyl group optionally having substituents (e.g., carbamoyl; carbamoyl group mono- or di-substituted by alkyl group having 1 to 6 carbon atoms such as methylcarbamoyl, dimethylcarbamoyl group etc., and the like), an amino group optionally having substituents (e.g., amino; amino group mono- or di-substituted by alkyl group having 1 to 6 carbon atoms such as methylamino, dimethylamino, ethylamino, diethylamino group etc., and the like) and the like can be mentioned, wherein the number of substituents and the position of the substitution are not particularly limited.

As the "benzene ring optionally having substituents" represented by ring C, a benzene ring is preferable.

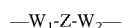
As the "aromatic monocyclic heterocycle" of the "aromatic monocyclic heterocycle optionally having substituents" represented by ring C, for example, a 5- or 6-membered aromatic monocyclic heterocycle such as furan, thiophene, pyrrole, oxazole, isoxazole, thiazole, isothiazole, imidazole, pyrazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, furazan, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, triazine etc., and the like can be mentioned. As the "aromatic monocyclic heterocycle" represented by ring C, a pyridine ring is particularly preferable. It may have, at substitutable positions thereof, 1 to 4 substituents similar to those for the "benzene ring optionally having substituents" represented by ring C.

The position where the "aromatic monocyclic heterocycle" of the "aromatic monocyclic heterocycle optionally having substituents" is condensed with the imidazole part is not particularly limited.

In the present invention, X<sub>1</sub> and X<sub>2</sub> represent an oxygen atom and a sulfur atom, respectively. Both X<sub>1</sub> and X<sub>2</sub> preferably represent an oxygen atom.

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In the present invention, W represents a "divalent chain hydrocarbon group optionally having substituents", or the formula:



wherein W<sub>1</sub> and W<sub>2</sub> are each a "divalent chain hydrocarbon group" or a bond, and Z is a divalent group such as a "divalent hydrocarbon ring group optionally having substituents", a "divalent heterocyclic group optionally having substituents", an oxygen atom, SO<sub>n</sub>, wherein n is 0, 1 or 2 or >N-E wherein E is a hydrogen atom, a hydrocarbon group optionally having substituents, a heterocyclic group optionally having substituents, a lower alkanoyl group, a lower alkoxy carbonyl group, an aralkyloxycarbonyl group, a thiocarbamoyl group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, a sulfamoyl group, a mono-lower alkylsulfamoyl group, a di-lower alkylsulfamoyl group, an arylsulfamoyl group, an arylsulfinyl group, an arylsulfonyl group, an arylcarbonyl group, or a carbamoyl group optionally having substituents, when Z is an oxygen atom, SO<sub>n</sub>, or >N-E, W<sub>1</sub> and W<sub>2</sub> are each a "divalent chain hydrocarbon group". Particularly, W is preferably a "divalent chain hydrocarbon group optionally having substituents".

As the "divalent chain hydrocarbon group" of the "divalent chain hydrocarbon group optionally having substituents" represented by W and "divalent chain hydrocarbon group" represented by W<sub>1</sub> and W<sub>2</sub>, for example, a C<sub>1-6</sub> alkylene group (e.g., methylene, ethylene, trimethylene etc.), a C<sub>2-6</sub> alkenylene group (e.g., ethenylene etc.), a C<sub>2-6</sub> alkynylene group (e.g., ethynylene etc.) and the like can be mentioned. The divalent chain hydrocarbon group for W may have 1 to 6 substituents similar to those for the "benzene ring optionally having substituents" represented by ring C at substitutable positions thereof.

As the "divalent chain hydrocarbon group" of the "divalent chain hydrocarbon group optionally having substituents" represented by W and "divalent chain hydrocarbon group" represented by W<sub>1</sub> and W<sub>2</sub>, a methylene group and an ethylene group are preferable. As W, an ethylene group is particularly preferable. When Z is an oxygen atom, SO<sub>n</sub>, or >N-E (n and E are as defined above), the "divalent chain hydrocarbon group" represented by W<sub>1</sub> is preferably a hydrocarbon group having 2 or more carbon atoms.

As the "hydrocarbon ring" of the "divalent hydrocarbon ring group optionally having substituents" represented by Z, for example, an alicyclic hydrocarbon ring, an aromatic hydrocarbon ring and the like can be mentioned, with preference given to one having 3 to 16 carbon atoms, which may have 1 to 4 substituents similar to those for the "benzene ring optionally having substituents" represented by ring C at substitutable positions thereof. As the hydrocarbon ring, for example, cycloalkane, cycloalkene, arene and the like are used.

As a cycloalkane in the "divalent hydrocarbon ring group optionally having substituents" represented by Z, for example, a lower cycloalkane and the like are preferable, and, for example, C<sub>3-10</sub> cycloalkane such as cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, bicyclo[2.2.1]heptane, adamantane etc., and the like are generally used.

As a cycloalkene in the "divalent hydrocarbon ring group optionally having substituents" represented by Z, for example, a lower cycloalkene is preferable, and, for example, C<sub>4-9</sub> cycloalkene such as cyclopropene, cyclobutene, cyclopentene, cyclohexene, cycloheptene, cyclooctene etc., and the like are generally used.

As an arene in the "divalent hydrocarbon ring group optionally having substituents" represented by Z, for example, a C<sub>6-14</sub> arene such as benzene, naphthalene, phenan-

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threne etc., and the like are preferable, and, for example, phenylene and the like are generally used.

As a heterocycle in the "divalent heterocyclic group optionally having substituents" represented by Z, a 5- to 12-membered "aromatic heterocycle" or "saturated or unsaturated non-aromatic heterocycle" containing, as ring-constituting atom (ring atom), 1 to 3 (preferably 1 or 2) kinds of at least 1 (preferably 1 to 4, more preferably 1 or 2) hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom etc., and the like can be mentioned, which may have 1 to 4 substituents similar to those for the "benzene ring optionally having substituents" represented by ring C at substitutable positions thereof.

As an aromatic heterocycle in the "divalent heterocyclic group optionally having substituents" represented by Z, an aromatic monocyclic heterocycle, an aromatic fused heterocycle and the like can be mentioned.

As the "aromatic monocyclic heterocycle", for example, a 5- or 6-membered aromatic monocyclic heterocycle such as furan, thiophene, pyrrole, oxazole, isoxazole, thiazole, isothiazole, imidazole, pyrazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, furazan, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, triazine etc., and the like can be mentioned.

As the "aromatic fused heterocycle", for example, a 8-to 12-membered aromatic fused heterocycle such as benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, indole, isoindole, 1H-indazole, benzimidazole, benzoxazole, 1,2-benzisoxazole, benzothiazole, 1,2-benzisothiazole, 1H-benzotriazole, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, phthalazine, naphthyridine, purine, pteridine, carbazole, carboline, acridine, phenoxazine, phenothiazine, phenazine, phenoxathiin, thianthrene, phenanthridine, phenanthroline, indolizine, pyrrolo[1,2-b]pyridazine, pyrazolo[1,5-a]pyridine, imidazo[1,2-a]pyridine, imidazo[1,5-a]pyridine, imidazo[1,2-b]pyridazine, imidazo[1,2-a]pyrimidine, 1,2,4-triazolo[4,3-a]pyridine, 1,2,4-triazolo[4,3-b]pyridazine etc., and the like can be mentioned.

As a saturated or unsaturated non-aromatic heterocycle in the "divalent heterocyclic group optionally having substituents" represented by Z, for example, a 3- to 8-membered (preferably 5- or 6-membered) saturated or unsaturated (preferably saturated) non-aromatic heterocycle (aliphatic heterocycle) such as oxylane, azetidine, oxetane, thietane, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, piperidine, tetrahydropyran, tetrahydrothiopyran, morpholine, thiomorpholine, piperazine, azepane, oxepane, thiene, oxazepane, thiazepane, azocane, oxocane, thiocane, oxazocane, thiazocane etc., and the like can be mentioned.

These may be oxo-substituted and may be, for example, 2-oxoazetidine, 2-oxopyrrolidine, 2-oxopiperidine, 2-oxazepane, 2-oxazocane, 2-oxotetrahydrofuran, 2-oxotetrahydropyran, 2-oxotetrahydrothiophene, 2-oxothiane, 2-oxopiperazine, 2-oxooxepane, 2-oxooxazepane, 2-oxothiepane, 2-oxothiazepane, 2-oxooxocane, 2-oxothiocane, 2-oxooxazocane, 2-oxothiazocane and the like.

The two bonds from the "hydrocarbon ring group" of the "divalent hydrocarbon ring group optionally having substituents" or the "heterocyclic group" of the "divalent heterocyclic group optionally having substituents" represented by Z may be present at any possible position.

The "hydrocarbon group optionally having substituents" and "heterocyclic group optionally having substituents" represented by E is as defined in the following.

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As the "lower alkanoyl group" represented by E, for example, formyl, a C<sub>1-6</sub> alkyl-carbonyl group such as acetyl, propionyl, butyryl, isobutyryl etc., and the like can be used.

As the "lower alkoxy-carbonyl group" represented by E, for example, a C<sub>1-6</sub> alkoxy-carbonyl group such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl etc., and the like are used.

As the "aralkyloxycarbonyl" represented by E, for example, a C<sub>7-11</sub> aralkyloxy-carbonyl group such as benzyloxycarbonyl etc., and the like are used.

As the "lower alkylsulfinyl group" represented by E, for example, a C<sub>1-6</sub> alkylsulfinyl group such as methylsulfinyl, ethylsulfinyl etc., and the like are used.

As the "lower alkylsulfonyl group" represented by E, for example, a C<sub>1-6</sub> alkylsulfonyl group such as methylsulfonyl, ethylsulfonyl etc., and the like are used.

As the "mono-lower alkylsulfamoyl group" represented by E, for example, a mono-C<sub>1-6</sub> alkylsulfamoyl group such as methylsulfamoyl, ethylsulfamoyl etc., and the like are used.

As the "di-lower alkylsulfamoyl group" represented by E, for example, a di-C<sub>1-6</sub> alkylsulfamoyl group such as dimethylsulfamoyl, diethylsulfamoyl etc., and the like are used.

As the "arylsulfamoyl group" represented by E, for example, a C<sub>6-10</sub> arylsulfamoyl group such as phenylsulfamoyl, naphthylsulfamoyl etc., and the like are used.

As the "arylsulfinyl group" represented by E, for example, a C<sub>6-10</sub> arylsulfinyl group such as phenylsulfinyl, naphthylsulfinyl etc., and the like are used.

As the "arylsulfonyl group" represented by E, for example, a C<sub>6-10</sub> arylsulfonyl group such as phenylsulfonyl, naphthylsulfonyl etc., and the like are used.

As the "arylcarbonyl group" represented by E, for example, C<sub>6-10</sub> aryl-carbonyl group such as benzoyl, naphthoyl etc., and the like are used.

The "carbamoyl group optionally having substituents" represented by E is, for example, a group of the formula CONR<sub>2</sub>R<sub>3</sub> wherein R<sub>2</sub> and R<sub>3</sub> are each a hydrogen atom, a hydrocarbon group optionally having substituents or a heterocyclic group optionally having substituents, and in the formula —CONR<sub>2</sub>R<sub>3</sub>, R<sub>2</sub> and R<sub>3</sub> may form a ring together with the adjacent nitrogen atom, and the like.

In the present invention, R is a "hydrocarbon group optionally having substituents" or a "heterocyclic group optionally having substituents", and R can be bonded to W. Of these, a C<sub>1-6</sub> hydrocarbon group optionally having substituents is preferable and a lower (C<sub>1-6</sub>) alkyl group is particularly preferable. The "hydrocarbon group optionally having substituents" and "heterocyclic group optionally having substituents" represented by R are as defined in the following. A detailed explanation of the case where R is bonded to W is given in the following.

In the present invention, D<sub>1</sub> and D<sub>2</sub> are each a bond, an oxygen atom, a sulfur atom or >NR<sub>1</sub>, and in the formula, R<sub>1</sub> is a hydrogen atom or a hydrocarbon group optionally having substituents. However, the present invention excludes a case where D<sub>1</sub> and D<sub>2</sub> are both respectively a bond. Among others, each of D<sub>1</sub> and D<sub>2</sub> is preferably a bond or an oxygen atom, and particularly preferably, D<sub>1</sub> is an oxygen atom and D<sub>2</sub> is an oxygen atom or a bond. The "hydrocarbon group optionally having substituents" represented by R<sub>1</sub> is as defined in the following.

In the present invention, G is a "hydrocarbon group optionally having substituents" or a "heterocyclic group optionally having substituents". Of these, a C<sub>1-6</sub> hydrocarbon group optionally having substituents or a saturated heterocyclic group optionally having substituents, which contains, as ring-constituting atom, 1 to 4 hetero atoms selected from oxygen

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atom, sulfur atom and nitrogen atom is preferable. As G, among others, a C<sub>1-6</sub> hydrocarbon group optionally having substituents or a saturated oxygen-containing heterocyclic group optionally having substituents, which further contains, as ring-constituting atom, 1 to 3 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom is preferable. The "hydrocarbon group optionally having substituents" and "heterocyclic group optionally having substituents" represented by G are as defined in the following.

As the "hydrocarbon group" of the "hydrocarbon group optionally having substituents" represented by the above-mentioned E, R, R<sub>1</sub> and G, for example, a saturated or unsaturated aliphatic hydrocarbon group, a saturated or unsaturated alicyclic hydrocarbon group, a saturated or unsaturated alicyclic-aliphatic hydrocarbon group, an aromatic hydrocarbon group, an aromatic-saturated or unsaturated alicyclic hydrocarbon group and the like can be mentioned, with preference given to those having 1 to 16, more preferably 1 to 6, carbon atoms. Specific examples thereof include alkyl group, alkenyl group, alkynyl group, cycloalkyl group, cycloalkenyl group, cycloalkylalkyl group, cycloalkenylalkyl group, aryl group and arylalkyl group and the like.

For example, the "alkyl group" is preferably a lower alkyl group (C<sub>1-6</sub> alkyl group) and the like, and, for example, a C<sub>1-6</sub> alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 1-ethylpropyl, hexyl etc., and the like are generally used. For R, a lower alkyl group (C<sub>1-6</sub> alkyl group) is preferable, particularly a methyl group is preferable.

For example, the "alkenyl group" is preferably a lower alkenyl group and the like, and, for example, a C<sub>2-7</sub> alkenyl group such as vinyl, 1-propenyl, allyl, isopropenyl, butenyl, isobutenyl, 2,2-dimethyl-pent-4-enyl etc., and the like are generally used.

For example, the "alkynyl group" is preferably a lower alkynyl group and the like, and, for example, a C<sub>2-6</sub> alkynyl group such as ethynyl, propargyl, 1-propynyl etc., and the like are generally used.

For example, the "cycloalkyl group" is preferably a lower cycloalkyl group and the like, and, for example, a C<sub>3-10</sub> cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptan-yl and adamantyl etc., and the like are generally used.

For example, the "cycloalkenyl group" is preferably a lower cycloalkenyl group, and, for example, a C<sub>3-10</sub> cycloalkenyl group such as cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, bicyclo[2.2.1]hept-5-en-2-yl etc., and the like are generally used.

For example, the "cycloalkylalkyl group" is preferably a lower cycloalkylalkyl group, and, for example, a C<sub>4-9</sub> cycloalkylalkyl group such as cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl and cyclohexylethyl etc., and the like are generally used.

For example, the "cycloalkenylalkyl group" is preferably a lower cycloalkenylalkyl group, and, for example, C<sub>4-9</sub> cycloalkenylalkyl such as cyclopentenylmethyl, cyclohexenylmethyl, cyclohexenylethyl, cyclohexenylpropyl, cycloheptenylmethyl, cycloheptenylethyl and bicyclo[2.2.1]hept-5-en-2-ylmethyl etc., and the like are generally used.

For example, the "aryl group" is preferably a C<sub>6-14</sub> aryl group such as phenyl, 1-naphthyl, 2-naphthyl, biphenyl, 2-anthryl etc., and the like, and, for example, phenyl group and the like are generally used.

The "arylalkyl group" contains, as the aryl moiety, the "aryl group" defined above, and as the alkyl moiety, the "alkyl group" defined above. Of these, for example, a C<sub>6-14</sub> aryl-C<sub>1-6</sub>

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alkyl group is preferable, and, for example, benzyl, phenethyl and the like are generally used.

As the substituent that the "hydrocarbon group" of the "hydrocarbon group optionally having substituents" represented by the above-mentioned E, R, R<sub>1</sub> and G may have, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine etc.), a nitro group, a cyano group, a hydroxy group, a thiol group, a sulfo group, a sulphino group, a phosphono group, an optionally halogenated lower alkyl group (e.g., C<sub>1-6</sub> alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 1-ethylpropyl, hexyl and the like, a mono-, di- or tri-halogeno-C<sub>1-6</sub> alkyl group such as chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, 6,6,6-trifluorohexyl etc., and the like), an oxo group, an amidino group, an imino group, an alkylenedioxy group (e.g., C<sub>1-3</sub> alkylenedioxy group such as methylenedioxy, ethylenedioxy etc., and the like), a lower alkoxy group (e.g., C<sub>1-6</sub> alkoxy group such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentyloxy, hexyloxy etc., and the like), an optionally halogenated lower alkoxy group (e.g., a mono-, di- or tri-halogeno-C<sub>1-6</sub> alkoxy group such as chloromethyloxy, dichloromethyloxy, trichloromethyloxy, fluoromethyloxy, difluoromethyloxy, trifluoromethyloxy, 2-bromoethyloxy, 2,2,2-trifluoroethyloxy, pentafluoroethyloxy, 3,3,3-trifluoropropoxy, 4,4,4-trifluorobutoxy, 5,5,5-trifluoropentyloxy, 6,6,6-trifluorohexyloxy etc., and the like), a lower alkylthio group (e.g., a C<sub>1-6</sub> alkylthio group such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, pentylthio, hexylthio etc., and the like), a carboxyl group, a lower alkanoyl group (e.g., formyl; a C<sub>1-6</sub> alkyl-carbonyl group such as acetyl, propionyl, butyryl, isobutyryl etc., and the like), a lower alkanoyloxy group (e.g., formyloxy; a C<sub>1-6</sub> alkyl-carbonyloxy group such as acetyloxy, propionyloxy, butyryloxy, isobutyryloxy etc., and the like), a lower alkoxy-carbonyl group (e.g., a C<sub>1-6</sub> alkoxy-carbonyl group such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl etc., and the like), an alkylalkoxy-carbonyl group (e.g., a C<sub>7-11</sub> alkylalkoxy-carbonyl group such as benzyloxy-carbonyl etc., and the like), a thiocarbonyl group, a lower alkylsulfinyl group (e.g., a C<sub>1-6</sub> alkylsulfinyl group such as methylsulfinyl, ethylsulfinyl etc., and the like), a lower alkyl-sulfonyl group (e.g., a C<sub>1-6</sub> alkylsulfonyl group such as methylsulfonyl, ethylsulfonyl etc., and the like), a sulfamoyl group, a mono-lower alkylsulfamoyl group (e.g., a mono-C<sub>1-6</sub> alkylsulfamoyl group such as methylsulfamoyl, ethylsulfamoyl etc., and the like), di-lower alkylsulfamoyl group (e.g., a di-C<sub>1-6</sub> alkylsulfamoyl group such as dimethylsulfamoyl, diethylsulfamoyl etc., and the like), an arylsulfamoyl group (e.g., a C<sub>6-10</sub> arylsulfamoyl group such as phenylsulfamoyl, naphthylsulfamoyl etc., and the like), an aryl group (e.g., a C<sub>6-10</sub> aryl group such as phenyl, naphthyl etc., and the like), an aryloxy group (e.g., a C<sub>6-10</sub> aryloxy group such as phenyloxy, naphthyloxy etc., and the like), an arylthio group (e.g., a C<sub>6-10</sub> arylthio group such as phenylthio, naphthylthio etc., and the like), an arylsulfinyl group (e.g., a C<sub>6-10</sub> arylsulfinyl group such as phenylsulfinyl, naphthylsulfinyl etc., and the like), an arylsulfonyl group (e.g., a C<sub>6-10</sub> arylsulfonyl group such as phenylsulfonyl, naphthylsulfonyl etc., and the like), an arylcarbonyl group (e.g., a C<sub>6-10</sub> aryl-carbonyl group such as benzoyl, naphthoyl etc., and the like), an arylcarbonyloxy group (e.g., a C<sub>6-10</sub> aryl-carbonyloxy group such as benzoyloxy, naphthoyloxy etc., and the like), an optionally halogenated lower alkylcarbonylamino group (e.g., an optionally halogenated C<sub>1-6</sub> alkyl-carbonylamino group such



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as acetylamino, trifluoroacetylamino etc., and the like), a carbamoyl group optionally having substituents (e.g., a group of the formula  $-\text{CONR}_2\text{R}_3$  wherein  $\text{R}_2$  and  $\text{R}_3$  are each a hydrogen atom, a hydrocarbon group optionally having substituents or a heterocyclic group optionally having substituents and in the formula  $-\text{CONR}_2\text{R}_3$ ,  $\text{R}_2$  and  $\text{R}_3$  may form a ring together with the adjacent nitrogen atom), an amino group optionally having substituents (e.g., a group of the formula  $-\text{NR}_2\text{R}_3$  wherein  $\text{R}_2$  and  $\text{R}_3$  are as defined above and in the formula  $-\text{NR}_2\text{R}_3$ ,  $\text{R}_2$  and  $\text{R}_3$  may form a ring together with the adjacent nitrogen atom), a ureido group optionally having substituents (e.g., a group of the formula  $-\text{NHCONR}_2\text{R}_3$  wherein  $\text{R}_2$  and  $\text{R}_3$  are as defined above and in the formula  $-\text{NHCONR}_2\text{R}_3$ ,  $\text{R}_2$  and  $\text{R}_3$  may form a ring together with the adjacent nitrogen atom), a carboxamide group optionally having substituents (e.g., a group of the formula  $-\text{NR}_2\text{COR}_3$  wherein  $\text{R}_2$  and  $\text{R}_3$  are as defined above), a sulfonamide group optionally having substituents (e.g., a group of the formula  $-\text{NR}_2\text{SO}_2\text{R}_3$  wherein  $\text{R}_2$  and  $\text{R}_3$  are as defined above), a heterocyclic group optionally having substituents (as defined for  $\text{R}_2$  and  $\text{R}_3$ ) and the like are used.

As the "hydrocarbon group" of the "hydrocarbon group optionally having substituents" for  $\text{R}_2$  and  $\text{R}_3$ , for example, a lower alkyl group (e.g., alkyl group having 1 to 6 carbon atoms such as methyl, ethyl, propyl group and the like), a lower alkenyl group (e.g., alkenyl group having 2 to 6 carbon atoms such as vinyl, allyl group and the like), a lower alkynyl group (e.g., alkynyl group having 2 to 6 carbon atoms such as ethynyl, propargyl group and the like), a cycloalkyl group (e.g., cycloalkyl group having 3 to 8 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl group and the like), a cycloalkenyl group (e.g., cycloalkenyl group having 3 to 8 carbon atoms such as cyclobutenyl, cyclopentenyl, cyclohexenyl group and the like), a cycloalkylalkyl group (e.g.,  $\text{C}_3\text{-C}_8$  cycloalkyl- $\text{C}_1\text{-C}_6$  alkyl group, such as cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl group and the like), a cycloalkenylalkyl group (e.g.,  $\text{C}_3\text{-C}_8$  cycloalkenyl- $\text{C}_1\text{-C}_6$  alkyl group, such as cyclobutenylmethyl, cyclopentenylmethyl, cyclohexenylmethyl group and the like), an aryl group (e.g., aryl group having 6 to 14 carbon atoms such as phenyl, naphthyl group and the like), an arylalkyl group (e.g.,  $\text{C}_6\text{-C}_{14}$  aryl- $\text{C}_1\text{-C}_6$  alkyl group, such as benzyl, naphthylmethyl group and the like) and the like can be mentioned.

As the "heterocyclic group" of the "heterocyclic group optionally having substituents" represented by  $\text{R}_2$  and  $\text{R}_3$ , a 5- to 12-membered monocyclic or fused heterocyclic group containing 1 or 2 kinds of 1 to 4 hetero atoms selected from nitrogen atom, sulfur atom and oxygen atom such as pyridyl, pyrrolidinyl, piperazinyl, piperidinyl, 2-oxazepinyl, furyl, decahydroisoquinolyl, quinolyl, indolyl, isoquinolyl, thienyl, imidazolyl, morpholinyl etc., and the like can be mentioned. As the substituent for the "hydrocarbon group optionally having substituents" and "heterocyclic group optionally having substituents" for  $\text{R}_2$  and  $\text{R}_3$ , for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine etc.), a lower alkyl group (e.g., alkyl group having 1 to 6 carbon atoms such as methyl, ethyl, propyl group and the like), a lower alkenyl group (e.g., alkenyl group having 2 to 6 carbon atoms such as vinyl, allyl group and the like), a lower alkynyl group (e.g., alkynyl group having 2 to 6 carbon atoms such as ethynyl, propargyl group and the like), a cycloalkyl group (e.g., cycloalkyl group having 3 to 8 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl group and the like), a lower alkoxy group (e.g., alkoxy group having 1 to 6 carbon atoms such as methoxy, ethoxy group and the like), a nitro group, a cyano group, a hydroxy group, a thiol group, a

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carboxyl group, a lower alkanoyl group (e.g., formyl;  $\text{C}_{1-6}$  alkyl-carbonyl group, such as acetyl, propionyl, butyryl group and the like), a lower alkanoyloxy group (e.g., formyloxy;  $\text{C}_{1-6}$  alkyl-carbonyloxy group, such as acetyloxy, propionyloxy group and the like), a lower alkoxy-carbonyl group (e.g.,  $\text{C}_{1-6}$  alkoxy-carbonyl group, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl group and the like), an aralkyloxy-carbonyl group (e.g.,  $\text{C}_{7-17}$  aralkyloxy-carbonyl group, such as benzyloxy-carbonyl group and the like), an aryl group (e.g.,  $\text{C}_{6-14}$  aryl group, such as phenyl, naphthyl group and the like), an aryloxy group (e.g.,  $\text{C}_{6-14}$  aryloxy group having, such as phenyloxy, naphthyloxy group and the like), an arylcarbonyl group (e.g.,  $\text{C}_{6-14}$  aryl-carbonyl group, such as benzoyl, naphthoyl group and the like), an arylcarbonyloxy group (e.g.,  $\text{C}_{6-14}$  aryl-carbonyloxy group, such as benzoyloxy, naphthoyloxy group and the like), a carbamoyl group optionally having substituents (e.g., carbamoyl; carbamoyl group mono- or di-substituted by alkyl group having 1 to 6 carbon atoms such as methylcarbamoyl, dimethylcarbamoyl group etc., and the like), an amino group optionally having substituents (e.g., amino; amino group mono- or di-substituted by alkyl group having 1 to 6 carbon atoms such as methylamino, dimethylamino, ethylamino, diethylamino group etc., and the like) and the like can be mentioned. The number and the position of the substitutions are not particularly limited.

As the ring formed by  $\text{R}_2$  and  $\text{R}_3$  together with the adjacent nitrogen atom, for example, pyrrolidine, piperidine, homopiperidine, morpholine, piperazine, tetrahydroquinoline, tetrahydroisoquinoline and the like can be mentioned.

The "hydrocarbon group" of the "hydrocarbon group optionally having substituents" represented by the above-mentioned E, R,  $\text{R}_1$  and G may have 1 to 5, preferably 1 to 3, the aforementioned substituent at substitutable positions of the hydrocarbon group, wherein, when the number of substituents is not less than 2, each substituents are the same or different.

As the "heterocyclic group" of the "heterocyclic group optionally having substituents" represented by the above-mentioned E, R and G, a 5- to 12-membered aromatic heterocyclic group and saturated or unsaturated non-aromatic heterocyclic group containing, as ring-constituting atom (ring atom), 1 to 3 (preferably 1 or 2) kinds of at least 1 (preferably 1 to 4, more preferably 1 to 3) hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom and the like can be mentioned. As the mentioned above, as the "heterocyclic group" of the "heterocyclic group optionally having substituents" represented by G, a saturated oxygen-containing heterocyclic group containing, as ring atoms, 1 to 4, more preferably 1 to 3, hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom etc., and the like are preferable, particularly a 5- to 12-membered saturated oxygen-containing heterocyclic group and the like are preferable.

As the "aromatic heterocyclic group", an aromatic monocyclic heterocyclic group, an aromatic fused heterocyclic group and the like can be mentioned.

As the "aromatic monocyclic heterocyclic group", for example, a 5- or 6-membered aromatic monocyclic heterocyclic group such as furyl, thienyl, pyrrolyl, oxazolyl, isooxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl etc., and the like can be mentioned.

As the "aromatic fused heterocyclic group", for example, a 8- to 12-membered aromatic fused heterocyclic group (pref-

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erably a heterocyclic group wherein the aforementioned 5- or 6-membered aromatic monocyclic heterocyclic group is condensed with a benzene ring, or a heterocyclic group wherein the same or different two heterocyclic groups of the aforementioned 5- or 6-membered aromatic monocyclic heterocyclic group are condensed), such as benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolyl, quinazolinyl, quinoxalyl, phthalazyl, naphthylidyl, purinyl, pteridinyl, carbazolyl,  $\alpha$ -carbolinyl,  $\beta$ -carbolinyl,  $\gamma$ -carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl etc., and the like can be mentioned.

As the "saturated or unsaturated non-aromatic heterocyclic group", for example, a 3- to 8-membered (preferably 5- or 6-membered) saturated or unsaturated (preferably saturated) non-aromatic heterocyclic group (aliphatic heterocyclic group) such as oxylanyl, azetidyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidinyl, tetrahydropyranyl, thianyl, morpholinyl, thiomorpholinyl, piperazinyl, azepanyl, oxepanyl, thiepanyl, oxazepanyl, thiazepanyl, azocanyl, oxocanyl, thiocanyl, oxazocanyl, thiazocanyl and the like can be mentioned. These may be oxo-substituted and examples thereof include 2-oxoazetidyl, 2-oxopyrrolidinyl, 2-oxopiperidinyl, 2-oxazepanyl, 2-oxazocanyl, 2-oxotetrahydrofuryl, 2-oxotetrahydropyranyl, 2-oxothiolanyl, 2-oxothianyl, 2-oxopiperazinyl, 2-oxooxepanyl, 2-oxooxazepanyl, 2-oxothiepanyl, 2-oxothiazepanyl, 2-oxooxocanyl, 2-oxothiocanyl, 2-oxooxazocanyl, 2-oxothiazocanyl and the like. A 5-membered non-aromatic heterocyclic group such as 2-oxopyrrolidinyl and the like is preferable.

As the substituent that the "heterocyclic group" of the "heterocyclic group optionally having substituents" represented by the above-mentioned E, R and G may have, for example, those similar to the "substituent" of the "hydrocarbon group optionally having substituents" represented by the aforementioned E, R, R<sub>1</sub> and G and the like are used.

The "heterocyclic group" of the "heterocyclic group optionally having substituents" represented by E, R and G may each have 1 to 5, preferably 1 to 3, substituents mentioned above at substitutable positions of the heterocyclic group, and when the number of substituents is two or more, the substituents are the same or different.

The bond between R and W in the compound of the present invention is explained below. When R and W are bonded, the position of the bond between R and W is not particularly limited as long as R and W can be bonded. The bondable position of R is the position where the "hydrocarbon group" and "substituent" of the "hydrocarbon group optionally having substituents" defined above for R can be bonded, and the position where the "heterocyclic group" and "substituent" of the "heterocyclic group optionally having substituents" defined above for R can be bonded.

As the bondable position of W, a bondable position of the "divalent chain hydrocarbon group" of the "divalent chain hydrocarbon group optionally having substituents" defined above for W, a bondable position of the "divalent chain hydrocarbon group" defined above for W<sub>1</sub> and W<sub>2</sub>, a bondable position of the "hydrocarbon ring" of the "hydrocarbon ring optionally having substituents" defined above for ring Z, and a bondable position of the "heterocyclic group" of the "het-

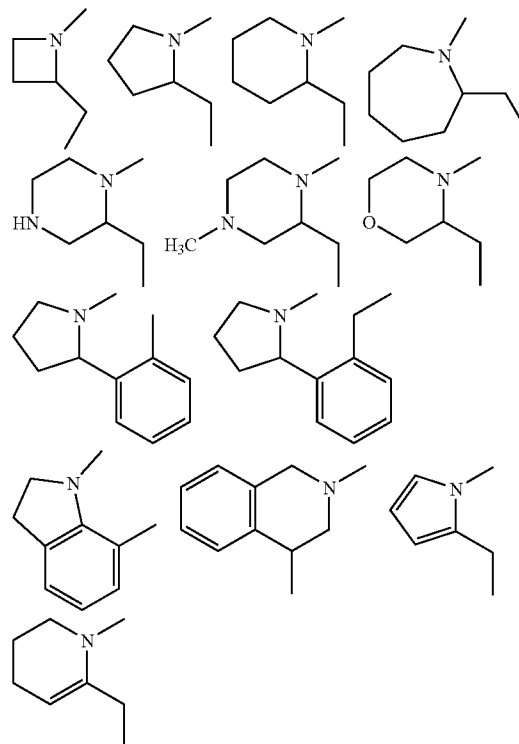
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erocyclic group optionally having substituents" defined above for ring Z can be mentioned.

R and W can be bonded at the bondable position thereof and can form a ring together with the adjacent nitrogen atom. As such ring, for example, a saturated nitrogen-containing ring (e.g., azetidine, pyrrolidine, piperidine, homopiperidine etc.), an unsaturated nitrogen-containing ring (e.g., tetrahydropyridine etc.), an aromatic nitrogen-containing ring (e.g., pyrrole etc.), a hetero ring (e.g., piperazine, morpholine etc.) containing, besides the nitrogen atom to which R and W are adjacent, at least one hetero atom selected from the group consisting of nitrogen, oxygen and sulfur, a fused ring (e.g., indole, indoline, isoindole, isoindoline, tetrahydroquinoline, tetrahydroisoquinoline etc.) and the like can be mentioned. Of these, a 4- to 7-membered ring is preferable.

The ring formed by R and W, which are bonded at each bondable position thereof, together with the adjacent nitrogen atom may have 1 to 4 substituents at substitutable positions thereof. When the number of substituents is 2 or more, the substituents are the same or different. As the substituent, the substituents of the "hydrocarbon group optionally having substituents" and "heterocyclic group optionally having substituents" defined for R, and the substituents of the "divalent chain hydrocarbon group optionally having substituents" defined for W can be mentioned. Specifically, a halogen atom (e.g., fluorine, chlorine, bromine, iodine etc.), a C<sub>1-6</sub> alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 1-ethylpropyl, hexyl etc., and the like can be mentioned.

By the bond between R and W, for example,



and the like are formed, but the ring is not limited to these. These may have substituents as defined above, and it would be understood for those of ordinary skill in the art that they may also have an isomer.



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In the present invention, X represents a leaving group, such as a halogen atom, a benzotriazolyl group, a (2,5-dioxypyrrolidin-1-yl)oxy group and the like. Of these, a halogen atom such as fluorine, chlorine, bromine, iodine and the like is preferable, and chlorine is particularly preferable.

In the present invention, M represents a hydrogen atom, a metal cation or a quaternary ammonium ion. In the present invention, the "metal cation" is exemplified by alkali metal ion (e.g., Na<sup>+</sup>, K<sup>+</sup>, Li<sup>+</sup>, Cs<sup>+</sup> and the like), with preference given to Na<sup>+</sup>.

In the present invention, the "quaternary ammonium ion" is exemplified by tetramethylammonium ion, tetraethylammonium ion, tetrapropylammonium ion, tetrabutylammonium ion and the like, with preference given to tetrabutylammonium ion.

In the compound (II), a pharmacologically acceptable basic salt can be formed between an acidic group in a molecule and an inorganic base or an organic base etc, and a pharmacologically acceptable acid addition salt can be formed between a basic group in a molecule and an inorganic acid or an organic acid etc.

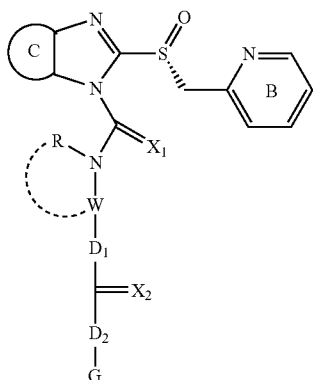
Examples of the inorganic basic salt of compound (II) include salt with alkali metal (e.g., sodium, potassium and the like), alkaline earth metal (e.g., calcium and the like), ammonia etc., and the like, and examples of the organic basic salt of compound (II) include salt with dimethylamine, triethylamine, piperazine, pyrrolidine, piperidine, 2-phenylethylamine, benzylamine, ethanolamine, diethanolamine, pyridine, collidine etc., and the like.

Examples of the acid addition salt of compound (II) include inorganic acid salt (e.g., hydrochloride, sulfate, hydrobromide, phosphate and the like), organic acid salt (e.g., acetate, trifluoroacetate, succinate, maleate, fumarate, propionate, citrate, tartrate, lactate, oxalate, methanesulfonate, p-toluenesulfonate and the like) and the like.

The compound (II) of the present invention encompasses hydrates. Examples of the "hydrate" include 0.5 hydrate-5.0 hydrate. Of these, 0.5 hydrate, 1.0 hydrate, 1.5 hydrate and 2.0 hydrate are preferable.

The compound (II) of the present invention encompasses racemates and optically active compounds. As the optically active compound, such compound wherein one enantiomer is in enantiomer excess (e.e.) of not less than 90% is preferable, more preferably in enantiomer excess of not less than 99%.

As an optically active form, an (R)-form represented by the formula:



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wherein each symbol is as defined above, is preferable. As the preferable compounds encompassed in compound (II), for example, the following specific compounds can be mentioned.

- That is,
- 2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate,
- 2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl trimethylacetate,
- 2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl cyclohexanecarboxylate,
- 2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl benzoate,
- 2-[methyl[[[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl benzoate,
- 2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl 4-methoxybenzoate,
- 2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl 3-chlorobenzoate,
- 2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl 3,4-difluorobenzoate,
- 2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl 4-trifluoromethoxybenzoate,
- 2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl 4-fluorobenzoate,
- 2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl 3,4,5-trimethoxybenzoate,
- 2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl 2-pyridinecarboxylate,
- 2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl methoxyacetate,
- ethyl 2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate,
- isopropyl 2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate,
- isopropyl 2-[methyl[[[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate,
- benzyl 2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate,
- 2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl tetrahydropyran-4-yl carbonate,
- 2-methoxyethyl 2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate,
- 2-[ethyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate,

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2-[isopropyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate,  
ethyl 2-[isopropyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate,  
2-[cyclohexyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate,  
2-[cyclohexyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl ethyl carbonate,  
2-[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](phenyl)amino]ethyl acetate,  
2-[[[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](phenyl)amino]ethyl acetate,  
tert-butyl 2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]-3-pyridyl]methyl carbonate,  
2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]benzyl acetate,  
2-[2-(acetyloxy)ethyl][[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate,  
[(2S)-1-[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]-2-pyrrolidinyl]methyl acetate,  
ethyl [methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]acetate,  
2-[[[5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methyl)amino]ethyl benzoate,  
3-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]propyl benzoate,  
2-[methyl[[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl tetrahydropyran-4-yl carbonate,  
ethyl 2-[methyl[[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate,  
ethyl 2-[methyl[[[(S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate,  
ethyl 2-[[[5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl]methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-yl]carbonyl](methyl)amino]ethyl carbonate,  
2-[[[5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl]methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-yl]carbonyl](methyl)amino]ethyl acetate,  
2-[[[5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl]methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-yl]carbonyl](phenyl)amino]ethyl acetate,  
4-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]butyl acetate,  
ethyl 4-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]butyl carbonate,  
ethyl 3-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]propyl carbonate,

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3-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]propyl acetate,  
3-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]propane-1,2-diyl diacetate,  
diethyl 3-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]propane-1,2-diyl biscarbonate,  
2-[[[5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl]methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-yl]carbonyl](methyl)amino]ethyl 3-chlorobenzoate,  
2-[methyl[[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate,  
2-ethoxyethyl 2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate,  
3-methoxypropyl 2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate,  
2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl N,N-dimethylglycinate,  
S-[2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl]thioacetate,  
ethyl 2-[2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethoxy]ethyl carbonate,  
ethyl 2-[methyl[[2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethoxy]carbonyl]amino]ethyl carbonate,  
ethyl 2-[[[5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methyl)amino]ethyl carbonate,  
2-[[[5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](phenyl)amino]ethyl acetate,  
ethyl 2-[[[(S)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methyl)amino]ethyl carbonate,  
ethyl 2-[[[2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methyl)amino]ethyl carbonate,  
2-[[[2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](phenyl)amino]ethyl acetate,  
2-[[[5-(difluoromethoxy)-2-[[[3,4-dimethoxy-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methyl)amino]ethyl ethyl carbonate,  
2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl 1-methylpiperidine-4-carboxylate,  
2-[[4-(aminocarbonyl)phenyl][[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate,  
2-[methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl 1-methyl-4-piperidinyl carbonate,  
2-[[4-(aminocarbonyl)phenyl][2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate,  
(-)-ethyl 2-[[[5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl]methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-yl]carbonyl](methyl)amino]ethyl carbonate and

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(+)-ethyl 2-[[[5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-yl]carbonyl](methylamino)ethyl carbonate, a salt thereof and the like can be mentioned.

Of these, the following compounds and salts thereof are preferable.

2-[methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate,

ethyl 2-[methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate,

2-[methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl tetrahydropyran-4-yl carbonate,

2-[methyl[[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl tetrahydropyran-4-yl carbonate,

ethyl 2-[methyl[[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate,

ethyl 2-[[[5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-yl]carbonyl](methylamino)ethyl carbonate,

2-[[[5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-yl]carbonyl](methylamino)ethyl acetate,

2-[methyl[[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate,

ethyl 2-[[[5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methylamino)ethyl carbonate,

ethyl 2-[[[(S)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methylamino)ethyl carbonate,

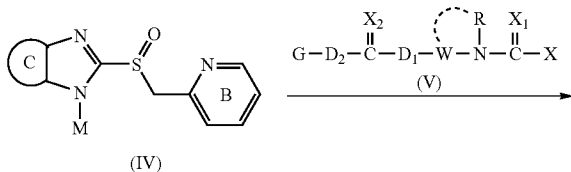
ethyl 2-[[[2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methylamino)ethyl carbonate, and

2-[[[5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methylamino)ethyl ethyl carbonate.

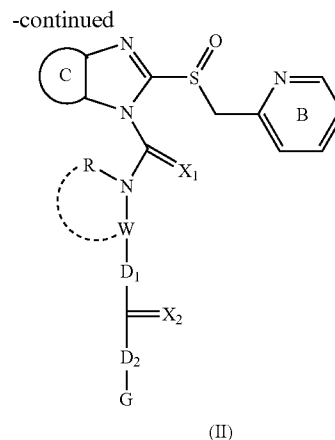
The compound (II) can be produced by the following method A or B.

(Method A)

The compound (II) or a salt thereof can be obtained by condensation of compound (IV) or a salt thereof with compound (V) or a salt thereof in the presence or absence of a base. The salt of compound (IV) and the salt of compound (V) here are exemplified by the above-mentioned salts of compound (II). For example, acid addition salts such as inorganic acid salt (e.g., hydrochloride, sulfate, hydrobromide, phosphate and the like), organic acid salt (e.g., acetate, trifluoroacetate, succinate, maleate, fumarate, propionate, citrate, tartrate, lactate, oxalate, methanesulfonate, p-toluenesulfonate and the like), and the like can be mentioned.



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wherein each symbol is as defined above. The reaction of Method A is generally conducted in a solvent, and a solvent that does not inhibit the reaction of Method A is selected as appropriate. Examples of such solvent include ethers (e.g., dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether, ethylene glycol dimethyl ether and the like), esters (e.g., ethyl formate, ethyl acetate, butyl acetate and the like), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride, trichlene, 1,2-dichloroethane and the like), hydrocarbons (e.g., n-hexane, benzene, toluene and the like), amides (e.g., formamide, N,N-dimethylformamide, N,N-dimethylacetamide and the like), ketones (e.g., acetone, methyl ethyl ketone, methyl isobutyl ketone and the like), nitrites (e.g., acetonitrile, propionitrile and the like), as well as dimethyl sulfoxide, sulfolane, hexamethylphosphoramide, water and the like, which may be used alone or as a mixed solvent. The amount of the solvent to be used is not particularly limited as long as the reaction mixture can be stirred, which is generally 2-to 100-fold amount by weight, preferably 5- to 50-fold amount by weight, relative to 1 mole of compound (IV) or a salt thereof.

The amount of compound (IV) or a salt thereof to be used is generally 1-10 mole, preferably 1-3 mole, relative to 1 mole of compound (IV) or a salt thereof. The reaction of Method A is carried out within a temperature range of from about 0° C. to 100° C., preferably 20° C. to 80° C.

The reaction time of Method A varies depending on the kind of compounds (IV), (V) or a salt thereof and solvent, reaction temperature and the like, but it is generally 1 min.-96 hrs., preferably 1 min.-72 hrs., more preferably 15 min.-24 hrs.

The base in Method A is, for example, an inorganic base (e.g., sodium carbonate, potassium carbonate, calcium carbonate, sodium hydrogen carbonate etc.), a tertiary amine (e.g., triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, pyridine, lutidine,  $\gamma$ -collidine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, 4-dimethylaminopyridine and the like); alkylene oxides (e.g., propylene oxide, epichlorohydrin etc.) and the like. The amount of the base to be used is generally 1 mole-10 mole, preferably 1 mole-3 mole, relative to 1 mole of compound (V) or a salt thereof.

The compound (IV) or a salt thereof can be produced according to the method described in JP-A-61-50978, U.S. Pat. No. 4,628,098 and the like or a method similar thereto.

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The compound (V) or a salt thereof can be produced according to a method known per se or a method analogous thereto. For example, when X is a chlorine atom, compound (V) can be obtained by reacting a compound represented by the formula (VII):

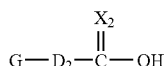


wherein each symbol is as defined above, or a salt thereof with phosgene, trichloromethyl chloroformate, bis(trichloromethyl)carbonate, thiophosgene and the like in the presence of an acid scavenger in a solvent (e.g., tetrahydrofuran, acetonitrile, dichloromethane etc.). Alternatively, compound (V) can be also obtained by treating ethylcarbamate, which is obtained by reacting compound (VII) or a salt thereof with ethyl chloroformate, with phosphorus oxychloride according to the method described in Synthetic Communications, vol. 17, p. 1887 (1987) or a method analogous thereto. As the salt of compound (VII), for example, acid addition salts such as inorganic acid salts (e.g., hydrochloride, sulfate, hydrobromide, phosphate etc.), organic acid salts (e.g., acetate, trifluoroacetate, succinate, maleate, fumarate, propionate, citrate, tartrate, lactate, oxalate, methanesulfonate, p-toluenesulfonate etc.), and the like can be mentioned.

As the acid scavenger used here, for example, inorganic bases (e.g., sodium carbonate, potassium carbonate, calcium carbonate, sodium hydrogen carbonate etc.), tertiary amine (e.g., triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, pyridine, lutidine,  $\gamma$ -collidine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, 4-dimethylaminopyridine etc.) and the like can be mentioned. The compound (VII) and a salt thereof can be produced according to a method known per se or a method analogous thereto. For example, when D<sub>1</sub> is other than a bond, compound (VII) can be obtained by condensing a compound represented by the formula (VIII):



wherein R<sub>4</sub> is a hydrogen atom or nitrogen-protecting group, and other symbols are as defined above, or a salt thereof with carboxylic acid or thionic acid represented by the formula (IX):

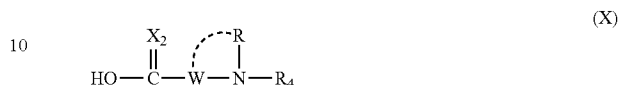


wherein each symbol is as defined above, or a reactive derivative thereof (e.g., anhydride, halide etc.), or a salt thereof in a suitable solvent (e.g., ethyl acetate, tetrahydrofuran, dichloromethane, N,N-dimethylformamide etc.), followed by deprotection as necessary. As the salt of compound (VIII), for example, acid addition salts such as inorganic acid salts (e.g., hydrochloride, sulfate, hydrobromide, phosphate etc.), organic acid salts (e.g., acetate, trifluoroacetate, succinate,

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maleate, fumarate, propionate, citrate, tartrate, lactate, oxalate, methanesulfonate, p-toluenesulfonate etc.) etc., and the like can be mentioned.

Alternatively, when D<sub>1</sub> is a bond, compound (VII) can be obtained by condensing carboxylic acid or thionic acid represented by the formula (X):



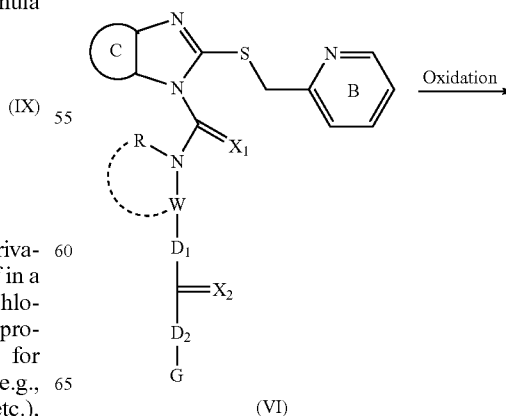
wherein each symbol is as defined above, or a reactive derivative thereof (e.g., anhydride, halide etc.), or a salt thereof with a compound represented by G-D<sub>2</sub>-H in a suitable solvent (e.g., ethyl acetate, tetrahydrofuran, dichloromethane, N,N-dimethylformamide etc.), followed by deprotection, as necessary. As the salt of compound (X), for example, acid addition salts such as inorganic acid salts (e.g., hydrochloride, sulfate, hydrobromide, phosphate etc.), organic acid salts (e.g., acetate, trifluoroacetate, succinate, maleate, fumarate, propionate, citrate, tartrate, lactate, oxalate, methanesulfonate, p-toluenesulfonate etc.) and the like, salts with alkali metal (e.g., sodium, potassium etc.), alkaline earth metal (e.g., calcium etc.), ammonia etc., and the like, and for example, organic base such as dimethylamine, triethylamine, piperazine, pyrrolidine, piperidine, 2-phenylethylamine, benzylamine, ethanolamine, diethanolamine, pyridine, collidine etc., and the like can be mentioned.

As the protecting group represented by R<sub>4</sub> in the formula (VIII) and the formula (X), for example, a formyl group, a C<sub>1-6</sub> alkyl-carbonyl group (e.g., acetyl, ethylcarbonyl etc.), a benzyl group, a tert-butyloxycarbonyl group, a benzyloxycarbonyl group, an allyloxycarbonyl group, a C<sub>7-10</sub> aralkyl-carbonyl group (e.g., benzylcarbonyl etc.), a trityl group and the like are used. These groups may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine etc.), a nitro group and the like.

As a method for removing such protecting groups, a method known per se or a method analogous thereto is used, which is, for example, a method using an acid, a base, reduction, UV light, palladium acetate etc., and the like are used.

(Method B)

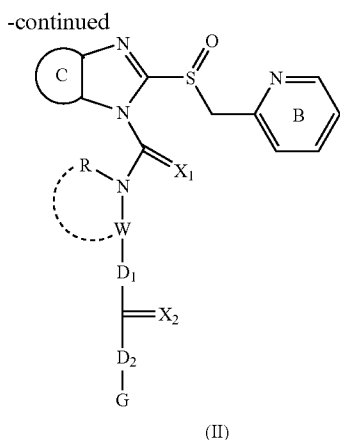
The compound (II) and a salt thereof can be obtained by subjecting compound (VI) or a salt thereof to oxidation reaction.





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wherein each symbol is as defined above.

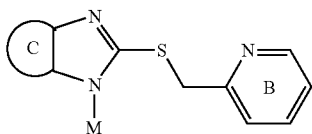
The reaction in Method B can be carried out using an oxidant such as nitric acid, hydrogen peroxide, peroxyacid, peroxyacid ester, ozone, dinitrogen tetroxide, iodosobenzene, N-halosuccinimide, 1-chlorobenzotriazole, tert-butyl hypochlorite, diazabicyclo[2.2.2]octane-bromine complex, sodium metaperiodate, selenium dioxide, manganese dioxide, chromic acid, cerium ammonium nitrate, bromine, chlorine, sulfonyl chloride, magnesium monoperoxyphthalate and the like. The amount of the oxidant to be used is generally 0.5 mole-2 mole, preferably 0.8 mole-1.2 mole, per 1 mole of compound (VI) or a salt thereof. The oxidation may be carried out using the above-mentioned oxidant such as hydrogen peroxide and peroxyacids in the presence of a catalyst such as vanadium acetate, vanadium oxide acetylacetonate, titanium tetraisopropoxide and the like.

The reaction of Method B is generally carried out in a solvent inert to the above-mentioned oxidation reaction. Examples of the "inert solvent" include water, alcohols (e.g., methanol, ethanol, 1-propanol, 2-propanol etc.), ketones (e.g., acetone, methyl ethyl ketone etc.), nitrites (e.g., acetonitrile, propionitrile etc.), amides (e.g., formamide, N,N-dimethylformamide etc.), ethers (e.g., diethyl ether, tert-butyl methyl ether, diisopropyl ether, dioxane, tetrahydrofuran etc.), sulfoxides (e.g., dimethyl sulfoxide etc.) and polar solvents (e.g., sulfolane, hexamethylphosphoramide etc.), which may be used alone or as a mixed solvent thereof. The "inert solvent" is used in generally 1- to 100-fold amount by weight of compound (VI) or a salt thereof.

The reaction temperature is generally from  $-80^{\circ}\text{C.}$  to  $80^{\circ}\text{C.}$ , preferably from  $0^{\circ}\text{C.}$  to  $30^{\circ}\text{C.}$

The reaction time is generally 1 min.-6 hrs., preferably 15 mins.-1 hr.

The compound (VI), which is a starting material in Method B, can be obtained by a reaction similar to that in Method A, by the use of, for example, a compound represented by the following formula (XI):



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wherein each symbol is as defined above, instead of compound (IV).

The compound (XI) can be synthesized according to the methods described in the following references or a method analogous thereto: JP-A-61-50978, JP-A-54-141783, JP-A-61-22079, JP-A-1-6270, JP-A-63-146882.

The salt of compound (VI) is exemplified by the above-mentioned salts of the compound (II), which are acid addition salts such as inorganic acid salt (e.g., hydrochloride, sulfate, hydrobromide, phosphate and the like), organic acid salt (e.g., acetate, trifluoroacetate, succinate, maleate, fumarate, propionate, citrate, tartrate, lactate, oxalate, methanesulfonate, p-toluenesulfonate and the like) and the like.

The compound (II) or a salt thereof obtained by the above-mentioned methods A or B can be isolated and purified from the reaction mixture by a separation means known per se (e.g., concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like). Since compound (II) and a salt thereof obtained by the above-mentioned methods A or B encompass any isomers thereof, optically pure compound (II) and a salt thereof can be obtained by, for example, subjecting compound (II) or a salt thereof to optical resolution, or asymmetric oxidation of compound (VI) or a salt thereof.

The method of optical resolution includes methods known per se, such as a fractional recrystallization method, a chiral column method, a diastereomer method, and so forth. Asymmetric oxidation includes methods known per se, such as the method described in WO96/02535 and the like.

The "fractional recrystallization method" includes a method in which a salt is formed between a racemate and an optically active compound [e.g., (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine, etc.], which salt is separated by fractional recrystallization etc., and, if desired, subjected to a neutralization process to give a free optical isomer.

The "chiral column method" includes a method in which a racemate or a salt thereof is applied to a column for optical isomer separation (chiral column). In the case of liquid chromatography, for example, optical isomers are separated by adding a racemate to a chiral column such as ENANTIO-OVM (produced by Tosoh Corporation), the DAICEL CHIRAL series (produced by Daicel Corporation) and the like, and developing the racemate in water, a buffer (e.g., phosphate buffer), an organic solvent (e.g., hexane, ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, triethylamine, etc.), or a solvent mixture thereof. In the case of gas chromatography, for example, a chiral column such as CP-Chirasil-DeX CB (produced by GL Science) and the like is used to separate optical isomers.

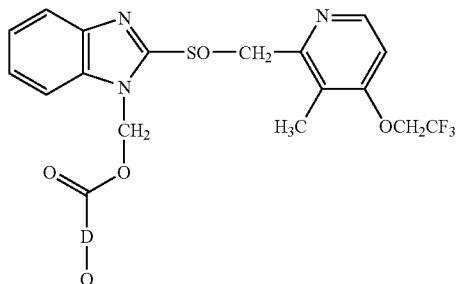
The "diastereomer method" includes a method in which a racemate and an optically active reagent are reacted to give a diastereomeric mixture, which is then subjected to ordinary separation means (e.g., fractional recrystallization, chromatography, etc.) to obtain either diastereomer, which is subjected to a chemical reaction (e.g., acid hydrolysis, base hydrolysis, hydrogenolysis, etc.) to cut off the optically active reagent moiety, whereby the desired optical isomer is obtained. Said "optically active reagent" includes, for example, optically active organic acids such as MTPA [ $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic acid], (-)-menthoxyacetic acid and the like, optically active alkoxymethyl halides such as (1R-endo)-2-(chloromethoxy)-1,3,3-trimethylbicyclo[2.2.1]heptane etc., and the like.



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Further, a benzimidazole compound represented by the following general formula (III) or a salt thereof is also mentioned as the specific example of the above-mentioned pro-drug.



In the above-mentioned formula (III), D indicates an oxygen atom or a bond, and Q indicates a hydrocarbon group optionally having a substituent group.

The "hydrocarbon group" of the "hydrocarbon group optionally having a substituent group" represented by Q includes an aliphatic or aromatic hydrocarbon group, and an aliphatic hydrocarbon group mentioned here means a saturated or unsaturated, linear, branched or cyclic hydrocarbon group. The hydrocarbon group is preferably a hydrocarbon group having 1 to 14 carbon atoms, and for example, a C<sub>1-6</sub> alkyl group, a C<sub>2-6</sub> alkenyl group, a C<sub>2-6</sub> alkynyl group, a C<sub>3-8</sub> cycloalkyl group and a C<sub>6-14</sub> aryl group are exemplified. A C<sub>1-6</sub> alkyl group, a C<sub>3-8</sub> cycloalkyl group and a C<sub>6-14</sub> aryl group are preferred, and above all a C<sub>1-6</sub> alkyl group and a C<sub>3-8</sub> cycloalkyl group are more preferred.

The above-mentioned "alkyl group" is a linear or branched alkyl group, preferably an alkyl group having 1 to 6 carbon atoms ("C<sub>1-6</sub> alkyl group") and for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, 1-methylpropyl, n-hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 3,3-dimethylpropyl, 2-ethylbutyl and the like are exemplified. An alkyl group having 1 to 4 carbon atoms is preferred. Among these, in Q, methyl, ethyl, isopropyl and tert-butyl are preferred, and tert-butyl is preferred particularly.

The above-mentioned "C<sub>2-6</sub> alkenyl group" is a linear or branched alkenyl group having 2 to 6 carbon atoms. Example thereof includes vinyl, n-propenyl, isopropenyl, n-butenyl, isobutenyl, sec-butenyl, tert-butenyl, n-pentenyl, isopentenyl, neopentenyl, 1-methylpropenyl, n-hexenyl, isohexenyl, 1,1-dimethylbutenyl, 2,2-dimethylbutenyl, 3,3-dimethylbutenyl, 3,3-dimethylpropenyl, 2-ethylbutenyl and the like. An alkenyl group having 2 to 4 carbon atoms is preferred and vinyl, n-propenyl and isopropenyl are preferred particularly.

The above-mentioned "C<sub>2-6</sub> alkynyl group" is a linear or branched alkynyl group having 2 to 6 carbon atoms. Example thereof includes ethynyl, n-propynyl (1-propynyl), isopropynyl (2-propynyl), n-butylnyl, isobutylnyl, sec-butylnyl, tert-butylnyl, n-pentynyl, isopentynyl, neopentynyl, 1-methylpropynyl, n-hexynyl, isohexynyl, 1,1-dimethylbutynyl, 2,2-dimethylbutynyl, 3,3-dimethylbutynyl, 3,3-dimethylpropynyl, 2-ethylbutynyl and the like. An alkynyl group having 2 to 3 carbon atoms is preferred and ethynyl, 1-propynyl and 2-propynyl are preferred particularly.

The above-mentioned "C<sub>3-8</sub> cycloalkyl group" is a cycloalkyl group having 3 to 8 carbon atoms. Example thereof includes cyclopropyl, cyclobutyl, cyclopentyl, cyclo-

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hexyl, cycloheptyl, cyclooctyl and the like. A cycloalkyl group having 5 to 7 carbon atoms is preferred and among them, cyclopentyl, cyclohexyl and cycloheptyl are preferred. Cyclohexyl is preferred particularly.

The above-mentioned "aryl group" is a monocyclic or condensed polycyclic aromatic hydrocarbon group, and preferably an aromatic hydrocarbon group having 6 to 14 carbon atoms ("C<sub>6-14</sub> aryl group"). Example thereof includes phenyl, naphthyl, anthryl, phenanthryl and acenaphthylenyl. An aromatic hydrocarbon group having 6 to 10 carbon atoms is preferred, and phenyl is particularly preferred in Q.

The above-mentioned "hydrocarbon group" may be substituted, and examples of the substituent group include, for example, a C<sub>6-14</sub> aryl group, a hydroxyl group, a halogen, an optionally halogenated C<sub>1-6</sub> alkoxy group, a C<sub>7-12</sub> aralkyloxy group, a C<sub>1-5</sub> alkoxy-carbonyl group, an optionally halogenated C<sub>1-6</sub> alkyl group, an amino group which may be substituted with a C<sub>1-6</sub> alkyl group, and the like.

Examples of the substituent group in the "alkyl group optionally having a substituent group" include, for example, an aryl group, a hydroxyl group, a halogen, an alkoxy group which may be substituted with 1 to 5 halogens, a C<sub>7-12</sub> aralkyloxy group, a C<sub>1-5</sub> alkoxy-carbonyl group, and the like. The number of said substituent group is 1 to 5 and preferably 1 to 3.

Examples of the substituent group in the "aryl group optionally having a substituent group" include a halogen, an alkyl group which may be substituted with 1 to 5 halogens, an aryl group, a hydroxyl group, an alkoxy group which may be substituted with 1 to 5 halogens, a C<sub>7-12</sub> aralkyloxy group, a C<sub>1-5</sub> alkoxy-carbonyl group, and the like. The number of said substituent group is 1 to 5 and preferably 1 to 3.

The above-mentioned "C<sub>1-6</sub> alkyl group", "C<sub>2-6</sub> alkenyl group" and "C<sub>2-6</sub> alkynyl group" may be substituted, and examples of the substituent group include (i) a C<sub>6-14</sub> aryl group, (ii) a hydroxyl group, (iii) a halogen, (iv) an optionally halogenated C<sub>1-6</sub> alkoxy group, (v) a C<sub>7-12</sub> aralkyloxy group, (vi) a C<sub>1-5</sub> alkoxy-carbonyl group, (vii) an acylamino group, (viii) an amino group which may be substituted with a C<sub>1-6</sub> alkyl group, and the like, and among these, (i) to (vii) are preferred. The number of said substituent group is 1 to 5 and preferably 1 to 3.

The above-mentioned "C<sub>3-8</sub> cycloalkyl group" and "C<sub>6-14</sub> aryl group" may be substituted, and examples of the substituent group include (i) a C<sub>6-14</sub> aryl group, (ii) a hydroxyl group, (iii) a halogen, (iv) an optionally halogenated C<sub>1-6</sub> alkoxy group, (v) a C<sub>7-12</sub> aralkyloxy group, (vi) a C<sub>1-5</sub> alkoxy-carbonyl group, (vii) a C<sub>1-6</sub> alkyl group which may be substituted with halogen, (viii) an amino group which may be substituted with a C<sub>1-6</sub> alkyl group, and the like, and among these, (i) to (vii) are preferred particularly. The number of said substituent group is 1 to 5 and preferably 1 to 3.

In the formula (III), Q is preferably a C<sub>1-6</sub> alkyl group, a C<sub>2-6</sub> alkenyl group and a C<sub>2-6</sub> alkynyl group, which may have a substituent group selected from a group consisting of (i) a C<sub>6-14</sub> aryl group, (ii) a hydroxyl group, (iii) a halogen, (iv) an optionally halogenated C<sub>1-6</sub> alkoxy group, (v) a C<sub>7-12</sub> aralkyloxy group, (vi) a C<sub>1-5</sub> alkoxy-carbonyl group and (vii) an acylamino group, or a C<sub>3-8</sub> cycloalkyl group or a C<sub>6-14</sub> aryl group, which may have a substituent selected from the group consisting of (i) a C<sub>6-14</sub> aryl group, (ii) a hydroxyl group, (iii) a halogen, (iv) an optionally halogenated C<sub>1-6</sub> alkoxy group, (v) a C<sub>7-12</sub> aralkyloxy group, (vi) a C<sub>1-5</sub> alkoxy-carbonyl group, and (vii) an optionally halogenated C<sub>1-6</sub> alkyl group.

Q is more preferably (1) a C<sub>1-6</sub> alkyl group which may have 1 to 5 substituent groups selected from the group consisting of (i) a C<sub>6-14</sub> aryl group, (ii) a hydroxyl group, (iii) a halogen,

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(iv) a C<sub>1-6</sub> alkoxy group which may be substituted with 1 to 5 halogens, (v) a C<sub>7-12</sub> aralkyloxy group and (vi) a C<sub>1-6</sub> alkoxy-carbonyl group, or (2) a C<sub>6-14</sub> aryl group which may have 1 to 5 substituent groups selected from the group consisting of (i) a halogen, (ii) a C<sub>1-6</sub> alkyl group which may be substituted with 1 to 5 halogens, (iii) a C<sub>6-14</sub> aryl group, (iv) a hydroxyl group, (v) a C<sub>1-6</sub> alkoxy group which may be substituted with 1 to 5 halogens, (vi) a C<sub>7-12</sub> aralkyloxy group and (vii) a C<sub>1-5</sub> alkoxy-carbonyl group.

Q is further more preferably a C<sub>1-6</sub> alkyl group which may have a substituent group selected from the group consisting of (i) a C<sub>6-14</sub> aryl group, (ii) a hydroxyl group, (iii) a halogen, (iv) an optionally halogenated C<sub>1-6</sub> alkoxy group, (v) a C<sub>7-12</sub> aralkyloxy group, (vi) a C<sub>1-5</sub> alkoxy-carbonyl group and (vii) an acylamino group; or a C<sub>3-8</sub> cycloalkyl group or a C<sub>6-14</sub> aryl group, which may have a substituent group selected from the group consisting of (i) a C<sub>6-14</sub> aryl group, (ii) a hydroxyl group, (iii) a halogen, (iv) an optionally halogenated C<sub>1-6</sub> alkoxy group, (v) a C<sub>7-12</sub> aralkyloxy group, (vi) a C<sub>1-5</sub> alkoxy-carbonyl group and (vii) an optionally halogenated C<sub>1-6</sub> alkyl group.

Among these, Q is preferably a C<sub>1-6</sub> alkyl group which may be substituted with a C<sub>6-14</sub> aryl group or a C<sub>6-14</sub> aryl group, and Q is preferably phenyl group, methyl or tert-butyl group in particular.

In compound (III), an acidic group in the molecule can form a pharmacologically acceptable base salt with an inorganic salt or an organic salt or the like, and a basic group in the molecule can form a pharmacologically acceptable acid additive salt with an inorganic salt or an organic salt or the like.

One preferable form of compound (III) of the present invention includes a compound wherein D is a bond and Q is an alkyl group optionally having a substituent group or an aryl group optionally having a substituent group.

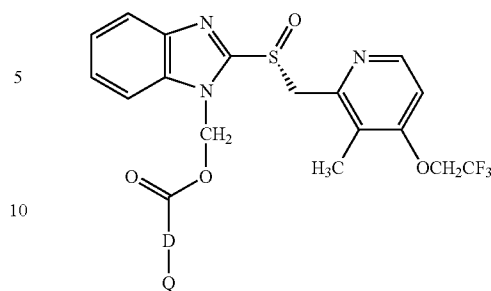
Examples of the inorganic base salt of compound (III) include, for example, salts with an alkali metal (for example, sodium, potassium and the like), an alkali earth metal (for example, calcium and the like), ammonia and the like, and Examples of the organic base salt of compound (III) include, for example, salts with dimethylamine, triethylamine, piperazine, pyrrolidine, piperidine, 2-phenylethylamine, benzylamine, ethanolamine, diethanolamine, pyridine, collidine and the like.

The acid additive salt of compound (III) includes, for example, inorganic acid salts (for example, hydrochloride, sulfate, hydrobromide, phosphate and the like), organic acid salts (for example, acetate, trifluoroacetate, succinate, maleate, fumarate, propionate, citrate, tartarate, lactate, oxalate, methanesulfoante, p-toluenesulfoante, and the like), etc.

The compound (III) of the present invention includes a hydrate. Said "hydrate" includes a 0.5 hydrate to 5.0 hydrates. Among these, 0.5 hydrate, 1.0 hydrate, 1.5 hydrates and 2.0 hydrates are preferred.

The compound (III) of the present invention includes a racemic compound and an optically active compound. As the optically active compound, such compound wherein one enantiomer is in enantiomer excess (e.e.) of not less than 90% is preferable, more preferably in enantiomer excess of not less than 99%. As an optically active form, an (R)-isomer represented by the formula:

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wherein each symbol is as defined above, is preferable.

The compound (III) can be produced by known methods per se, and are produced by the methods disclosed in, for example, JP-A 2002-187890, WO 02/30920 and the like, or analogous methods thereto. Further, the optically active compound (III) can be obtained by optical resolution methods (a fractional recrystallization method, a chiral column method, a diastereomer method, a method using microorganism or enzyme, and the like) and an asymmetric oxidation method, etc. As the PPI of other benzimidazole derivative, the present invention can be applied to the compound disclosed in WO 03/27098.

Although the compounding amounts of the active ingredient represented by the general formulae (I'), (I), (II) and (III) used in the present invention differ depending on the kinds and doses of the active ingredient, the amounts are, for example, about 1% by weight to about 60% by weight based on the total amount of tablets or granules of the present invention, preferably about 1% by weight to about 50% by weight and further preferably about 8% by weight to about 40% by weight. When the active ingredient is a benzimidazole compound PPI, in particular lansoprazole, the amount is about 8% by weight to about 40% by weight.

In case of capsules containing the imidazole PPI, especially benzimidazole PPI represented by the general formula (I') or (I) such as lansoprazole or an optically active compound thereof (R-isomer and the like) and the imidazole derivative PPI represented by the formula (II) and (III), 2 kinds or more of a tablet, granule or fine granule having different behavior of release (for example, 2 kinds of granules such as granules wherein the active ingredient is released comparatively quickly and granules wherein the active ingredient is released with prolonged time) may be filled in combination, using release-controlled coating-layers which have different release properties and conditions respectively. Further, 2 kinds of these release-controlled coating-layers may be stacked in 2 or more layers in the respective granules or fine granules. The preparation which enhances blood levels at a more earlier stage after administration to reveal drug efficacy and then sustain the drug efficacy by the expression of the drug efficacy of the release-controlled granule can be provided, by preparing a preparation (preferably a capsule) which contains a granule having an intermediate layer on the core particle containing the above-mentioned active ingredient and only one layer of enteric coat on said intermediate layer (accordingly, among the above-mentioned release-controlled granule or fine granule by the present invention, the granule in which the release of active ingredient is comparatively rapid.), in addition to a tablet, granule or fine granule having the release-controlled coating-layers of the present invention and the digestive tract retentive gel-forming polymer; or by administering capsules containing a tablet, granule

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or fine granule having the release control layer of the present invention and the digestive tract retentive gel-forming polymer, together with a preparation containing only granules having a usual enteric coat. Further, when the tablet (in this case, small size tablet is preferable), granule or fine granule to be filled has an enough release-controlling function, the capsules of the present invention may not always contain the gel-forming polymer. Capsules may be prepared using only the release-controlled tablet, granule or fine granule, or by combining the release-controlled tablet, granule or fine granule with a fast-releasing type granule having only enteric coat. In case of such combined preparations and combined administration, there can be prepared the preparations by which the blood level is preferably enhanced at a more earlier stage to achieve drug efficacy and to reach the first maximal blood level, and then the second maximal blood level is reached by the release of active ingredient from granules in which the release was controlled, that is, two peaks are expressed. Further, the controlled release preparation such as the above-mentioned controlled release capsule of the present invention and a usual capsule wherein the active ingredient is comparatively released quickly may be administered at the same time or at an interval. A high blood level of active ingredient can be maintained over a long time by such combined administration.

Usual enteric-coated Granules can be produced, for example, according to the method described in JP-A 63-301826. Further, it is preferable to prepare a stabilized preparation according to the method described in JP-A 62-277322.

Further, the granule which contains lansoprazole or optically active form thereof and the like at a higher concentration and is sufficiently stabilized can be produced as follow. Namely, there are produced the granules having an active ingredient layer, an intermediate layer formed on said active ingredient layer and an enteric coated layer formed on said intermediate layer, wherein said active ingredient layer contains about 10% by weight to about 40% by weight of lansoprazole and the like based on the total amount of the granule and a basic inorganic salt as a stabilizer and average particle diameter is about 600  $\mu\text{m}$  to about 2500  $\mu\text{m}$ , using known granulation methods such as a fluid-bed granulation method (for example, a centrifugal fluid-bed granulation method), a fluidized granulation method and a stirring granulation method (for example, a fluid-bed fluidized granulation method).

Specifically, the active ingredient layer can be obtained, for example, by coating a core particle with a dusting powder containing the imidazole PPI, a basic metal salt, an excipient, a disintegrant and the like while spraying a binding solution such as hydroxypropylcellulose and the like on the core particle. As said core particle, for example, Nonpareil prepared by coating sucrose (75 parts by weight) with corn starch (25 parts by weight) by a known method per se, a spherical core granule using crystalline cellulose and the like are exemplified. Further, a core granule itself may be the above-mentioned active ingredient of drug. The average particle size of said granules is 14 to 80 mesh in general.

As the core, a spherically granulated product of sucrose and starch, a spherically granulated product of crystalline cellulose, a spherically granulated product of crystalline cellulose and lactose and the like are exemplified.

The ratio of coating layer relative to the core can be selected within a range of being able to control the elution property of active ingredient and the particle size of granules.

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For example, it is usually about 0.2 part by weight to about 5 parts by weight based on 1 part by weight of core, and preferably about 0.1 part by weight to about 5 parts by weight.

Then, the intermediate layer is formed on the active ingredient layer obtained by a conventional method. For example, the component of the intermediate layer is diluted with purified water and the like, and the mixture is sprayed in liquid form to coat the active ingredient layer. At this time, it is preferable to coat the layer while spraying a binding agent such as hydroxypropylcellulose. Examples of the intermediate layer include, for example, a layer in which sugars such as sucrose (purified white sugar (those pulverized (powder sugar) and those not pulverized) and the like), starch sugar such as corn starch, lactose, honey and sugar alcohol (D-mannitol, erythritol and the like) are appropriately compounded with polymeric base materials such as low substituted hydroxypropylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose (for example, TC-5 and the like), polyvinyl pyrrolidone, polyvinyl alcohol, methylcellulose and hydroxyethyl methylcellulose. Excipients (for example, masking agent (titanium oxide and the like)) and antistatic agents (titanium oxide, talc and the like) which are added to prepare a preparation may be further appropriately added in the intermediate coating layer, if necessary.

The coat amount of the intermediate coating layer is usually, for example, about 0.02 part by weight to about 1.5 parts by weight based on 1 part by weight of granules containing the benzimidazole PPI, and preferably about 0.05 part by weight to about 1 part by weight.

Further, the granules which contain lansoprazole and the like at a high concentration and are sufficiently stabilized can be produced by forming a enteric coated layer on the intermediate coating layer by a conventional method. As the component of the enteric coated layer, for example, sustained release base materials such as aqueous enteric polymer base materials such as cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate, hydroxymethylcellulose acetate succinate, ethyl acrylate-methyl methacrylate-trimethylammoniummethyl methacrylate chloride copolymer (Eudragit RS or RL; manufactured by Rohm Co.), methyl methacrylate-ethyl acrylate copolymer (Eudragit NE30D; manufactured by Rohm Co.), carboxymethyl ethylcellulose and shellac; plasticizers such as water-soluble polymer, triethyl citrate, polyethylene glycol (polyethylene glycol 6000 (trade name: Macrogol 6000, and the like), acetylated monoglyceride, triacetin and castor oil are used. These may be used alone or by mixing 2 kinds or more.

The coat amount of the enteric coated layer is about 10% by weight to about 70% by weight based on the total amount of granules before enteric coating, preferably about 10% by weight to about 50% by weight and more preferably about 15% by weight to about 30% by weight.

In case of a tablet, for example, the benzimidazole compound, an excipient, a binding agent, a disintegrant, a lubricant and the like are mixed to directly produce tables by compression, or the granules which is produced in same manner as the above-mentioned granules can be compressed into tablet. Further, alternatively, 2 layered tablets may be prepared with a commercially available multilayer tablet machine using the granulated granules.

Among the preparations of the present invention, preparations containing the PPI of benzimidazole compound represented by the general formula (I') such as lansoprazole and optically active form thereof, above all benzimidazole PPI compound represented by the general formula (I), and the PPI of a prodrug-type imidazole compound derivative (in particular, a compound represented by the above-mentioned general



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formula (II) and (III) and an optically active compound thereof have superior anti-ulcer effect, gastric juice secretion suppressing effect, mucosa protective effect, anti-*Helicobacter pylori* effect and the like in vivo, and are useful as a medicine because of low toxicity. In particular, since the imidazole compound represented by the above-mentioned general formula (II) is stable to an acid, it is unnecessary to prepare an enteric preparation for oral administration, the cost of preparing enteric preparations is reduced, and the patients with weak deglutition, in particular, aged people and children are easily dosed because the size of the preparations becomes small. Further, since the absorption is faster than enteric preparations, gastric juice secretion suppressing effect is rapidly expressed, and since it is gradually converted to its original compound in vivo, it has a sustainability and is useful as anti-ulcer agents and the like. The PPI compound of compound (I') of the present invention or a salt thereof is less toxic, and can be orally or parenterally (for example, local, rectal, vein administration) and safely administered as it is or as a pharmaceutical composition by mixing with a pharmacologically acceptable carrier according to a known method per se, that is, for example, as a preparation such as a tablet (including sugar coated tablet and film coated tablet), powder, granule, capsule (including soft capsule), intraoral disintegrating tablet, liquid, injection, suppository, sustained-release agent and liniment.

The tablet, granule or fine granule of the present invention can be orally administrated to mammals (for example, human, monkey, sheep, horse, dog, cat, rabbit, mouse and the like) for the treatment and prevention of digestive ulcer (for example, gastric ulcer, duodenum ulcer, marginal ulcer and the like), Zollinger-Ellison syndrome, gastritis, reflux esophagitis, Symptomatic Gastroesophageal Reflux Disease (symptomatic GERD) with no esophagitis, NUD (Non Ulcer Dyspepsia), gastric cancer (including gastric cancer accompanied with the production promotion of interleukin-1 $\beta$  caused by gene polymorphism of interleukin-1), gastric MALT lymphoma and the like; the eradication of *Helicobacter pylori*, the suppression of upper digestive tract hemorrhage caused by the digestive ulcer, acute stress ulcer and hemorrhagic gastritis; the suppression of upper digestive tract hemorrhage caused by invasive stress (stress caused by major operation which requires intensive management after operation and by cerebro-vascular accident, head lesion, multiorgan disorder and wide range burn which require intensive care), and the treatment and prevention of ulcer caused by non steroid anti-inflammatories; the treatment and prevention of hyperchylia and ulcers caused by stress after operation, etc. The granules and capsules of the present invention may be used in combination with other active ingredients (for example, 1 to 3 active ingredients) for the eradication of *Helicobacter pylori* and the like.

Examples of the "other active ingredients" include, for example, an antibacterial such as an anti-*Helicobacter pylori* active substance, an imidazole compound and a quinolone compound, and bismuth salts. In particular, pharmaceuticals obtained by combining the granules and capsules of the present invention with the antibacterials are preferable. Among these, the combination with an antibacterial such as an anti-*Helicobacter pylori* active substance and an imidazole compound is preferable. Examples of the anti-*Helicobacter pylori* active substance include, for example, penicillin antibiotic (for example, amoxicillin, benzylpenicillin, piperacillin, mecillinam and the like), cephem antibiotic (for example, cefixime, cephachlor and the like), macrolide antibiotic (for example, erythromycin antibiotic such as erythromycin and clarithromycin), tetracycline antibiotic (for example, tetracy-

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cline, minocycline, streptomycin and the like), aminoglycoside antibiotic (for example, gentamicin, amikacin and the like), imipenem etc. In particular, penicillin antibiotic, macrolide antibiotic and the like are preferred.

Examples of the "imidazole compound" include, for example, metronidazole, miconazole and the like. Examples of the "bismuth salt" include, for example, there are mentioned bismuth acetate, bismuth citrate and the like. The antibacterial of "quinolone compound" is also preferable, and for example, ofloxacin, ciprofloxacin and the like are exemplified. In particular, it is preferable to use the granules and capsules of the present invention together with penicillin antibiotic (for example, amoxicillin and the like) and/or erythromycin antibiotic (for example, clarithromycin and the like) for the eradication of *Helicobacter pylori*.

Further, for example, in case of lansoprazole, capsules containing 15 mg of crystalline lansoprazole have been often filled in No.3 capsules, and capsules containing 30 mg have been often filled in No.1 capsules. However, the granules containing an active ingredient at high concentration are unexpectedly obtained by providing an intermediate coating layer, compounding a basic inorganic salt stabilizer and further controlling the particle size of granules without damaging the stability of the active ingredient and preparation. Thus, since the amount of components other than the active ingredient can be reduced, capsules containing 15 mg can be miniaturized to No.4 to No.5 capsules and capsules containing 30 mg can be miniaturized to No.3 to No.5 capsules. Further, No.1 to No.3 capsule can be also used for the capsule containing 60 mg.

Further, in case of the optically active compound of lansoprazole, No.3 to No.5 capsule, No.2 to No.4 capsule and No.1 to No.3 capsule can be used for the capsule containing 30 mg, 40 mg and 60 mg respectively.

For example, since the capsule containing 60 mg of lansoprazole or lansoprazole R-isomer contains the active ingredient at high concentration and the capsule is miniaturized, it is easy to take and suitable for treatment of acid excessive secretion symptom including Zollinger-Ellison syndrome in particular.

Dose per day differs depending on the extent of symptom, age for administration objective, sexuality, body weight, timing of administration, interval, the kind of active ingredient and the like, and are not specifically limited. For example, when the drug is orally administrated to adults (60 kg) as an anti-ulcer agent, the dose is about 0.5 to 1500 mg/day and preferably about 5 to 150 mg/day as active ingredient. These preparations containing these benzimidazole or imidazole compound may be divided to administer once a day or 2 to 3 times a day.

Further, the form of package may be also stabilized in order to improve the stability of the solid preparation of the present invention at storage or transportation. For example, the stabilization of the capsule preparation containing the benzimidazole or imidazole compound of the present invention can be improved by using package form such as package suppressing the permeation of oxygen and moisture, package replaced with gas (namely, package replaced with gas other than oxygen), vacuum package and package enclosed with a deoxidizer. The stabilization is improved by reducing oxygen



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amount with which the solid preparation is directly brought in contact, using these package forms. When a deoxidizer is enclosed, the pharmaceutical solid preparation is packed with an oxygen permeating material, and then another packing may be carried out together with the package.

## EXAMPLES

The present invention is explained in detail in the following by referring to Reference Examples, Synthetic Examples, Examples and Experiment Examples. The present invention is not limited by the Examples.

The corn starch, hydroxypropyl cellulose (HPC-L), polyethylene glycol 6000 and titanium oxide used in the following Examples of Preparation are the conformed materials to the 14th revised Japanese Pharmacopoeia.

In the following Reference Examples and Synthetic Examples, room temperature means about 15-30° C.

<sup>1</sup>H-NMR spectra were determined with CDCl<sub>3</sub>, DMSO-d<sub>6</sub> and CD<sub>3</sub>OD as the solvent using Varian Gemini-200 and Mercury-300; data are shown in chemical shift δ (ppm) from the internal standard tetramethylsilane.

Other symbols in the present specification mean the following.

s: singlet

d: doublet

t: triplet

q: quartet

m: multiplet

br: broad

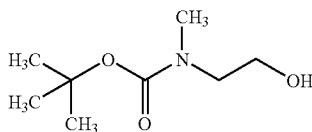
bs: broad singlet

bm: broad multiplet

J: coupling constant

## Reference Example 1

tert-Butyl 2-hydroxyethyl(methyl)carbamate



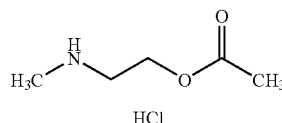
To a mixture of 2-(methylamino)ethanol (30.04 g) and ethyl acetate (90 mL) was dropwise added a mixture of di-tert-butyl dicarbonate (87.30 g) and ethyl acetate (10 mL) under ice-cooling. After stirring at room temperature for 2 hrs., the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (150 mL), washed with water (100 mL) and dried over anhydrous magnesium sulfate. Concentration under reduced pressure gave the title compound (66.19 g) as a colorless oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.47(9H,s), 2.92(3H,s), 3.40(2H,t, J=5.1 Hz), 3.72-3.80(2H,m).

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## Reference Example 2

2-(Methylamino)ethyl acetate hydrochloride

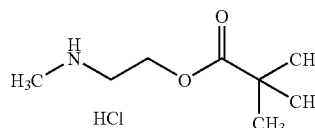


To a mixture of 2-(methylamino)ethanol (1.50 g) and ethyl acetate (20 mL) was added di-tert-butyl dicarbonate (4.37 g) under ice-cooling. After stirring under ice-cooling for 1.5 hrs., acetic anhydride (2.08 mL), pyridine (1.78 mL) and 4-dimethylaminopyridine (0.12 g) were added. After stirring at room temperature for 2 hrs., ethyl acetate (50 mL) was added to the reaction mixture, and the mixture was washed with water (50 mL), a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL). After drying over anhydrous magnesium sulfate, the mixture was concentrated under reduced pressure. To the residue was added a 4N hydrogen chloride—ethyl acetate solution (20 mL), and the mixture was stirred at room temperature for 2 hrs. Diethyl ether (10 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (2.93 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 2.07(3H,s), 2.53(3H,s), 3.12-3.17(2H,m), 4.24-4.30(2H,m), 9.29(2H,br).

## Reference Example 3

2-(Methylamino)ethyl trimethylacetate hydrochloride



To a mixture of tert-butyl 2-hydroxyethyl(methyl)carbamate (1.75 g) obtained in Reference Example 1 and ethyl acetate (15 mL) was added triethylamine (1.67 mL) and a mixture of trimethylacetyl chloride (1.35 mL), and ethyl acetate (5 mL) was dropwise added. After stirring at room temperature for 2 hrs., pyridine (1.62 mL) was added, and the mixture was stirred overnight at room temperature. Ethyl acetate (50 mL) was added to the reaction mixture, and the mixture was washed with water (50 mL), a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, a 4N hydrogen chloride—ethyl acetate solution (10 mL) was added to the residue. After stirring at room temperature for 2 hrs., diethyl ether (10 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (1.65 g) as a white solid.

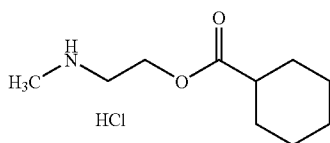
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<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.18(9H,s), 2.56(3H,s), 3.17(2H,t, J=10.5 Hz), 4.22-4.28(2H,m), 9.19(2H,br).

## Reference Example 4

## 2-(Methylamino)ethyl cyclohexanecarboxylate hydrochloride

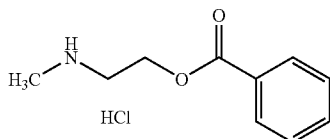


To a mixture of tert-butyl 2-hydroxyethyl (methyl)carbamate (1.75 g) obtained in Reference Example 1 and ethyl acetate (20 mL) were added pyridine (0.97 mL) and 4-dimethylaminopyridine (catalytic amount), and cyclohexanecarbonyl chloride (1.60 mL) was dropwise added. After stirring at room temperature for 2 hrs., pyridine (0.65 mL) and cyclohexanecarbonyl chloride (0.58 mL) were added, and the mixture was stirred overnight at room temperature. Ethyl acetate (50 mL) was added to the reaction mixture, and the mixture was washed with water (50 mL), a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, a 4N hydrogen chloride—ethyl acetate solution (10 mL) was added to the residue. After stirring at room temperature for 2 hrs., diethyl ether (10 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (1.88 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.10-1.45(5H,m), 1.54-1.73(3H,m), 1.83-1.93(2H,m), 2.29-2.42(1H,m), 2.54(3H,s), 3.12-3.18(2H,m), 4.23-4.29(2H,m), 9.23(2H,br).

## Reference Example 5

## 2-(Methylamino)ethyl benzoate hydrochloride



To a mixture of 2-(methylamino)ethanol (30.04 g) and ethyl acetate (90 mL) was dropwise added a mixture of di-tert-butyl dicarbonate (87.30 g) and ethyl acetate (10 mL) under ice-cooling. After stirring at room temperature for 1 hr., benzoyl chloride (61.8 g) and pyridine (38.8 mL) were added under ice-cooling. After stirring at room temperature for 1 hr., a solid was filtered off. The solid was washed with ethyl acetate (100 mL) and the filtrate and the washing were combined, which was washed with water (100 mL) and saturated brine (100 mL). After drying over anhydrous magnesium sulfate, the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (100 mL), a 4N hydrogen chloride—ethyl acetate solution (200 mL) was added, and the mixture was stirred at room temperature for 30 min. Diethyl ether (100 mL) was added and a solid was

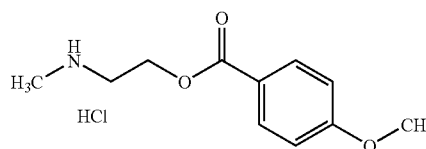
## 52

collected by filtration. The solid was washed twice with ethyl acetate (100 mL) and dried under reduced pressure at 60° C. to give the title compound (57.4 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 2.62(3H,s), 3.32(2H,m), 4.53(2H,t, J=9.9 Hz), 7.51-7.57(2H,m), 7.68(1H,m), 8.11(2H,d, J=7.8 Hz), 9.26(2H,bs).

## Reference Example 6

## 2-(Methylamino)ethyl 4-methoxybenzoate hydrochloride

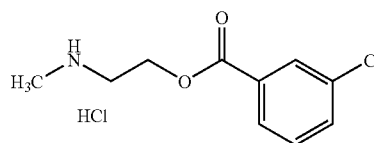


To a mixture of tert-butyl 2-hydroxyethyl (methyl)carbamate (1.75 g) obtained in Reference Example 1 and ethyl acetate (10 mL) were added 4-methoxybenzoyl chloride (1.88 g) and pyridine (0.97 mL). After stirring at room temperature for 14 hrs., 4-methoxybenzoyl chloride (0.70 g) and pyridine (0.97 mL) were added and the mixture was stirred at room temperature for 1 hr. Ethyl acetate (80 mL) was added to the reaction mixture, and the mixture was washed with water (20 mL), a saturated aqueous sodium hydrogen carbonate solution (20 mL) and water (20 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in ethyl acetate (10 mL), and a 4N hydrogen chloride—ethyl acetate solution (10 mL) was added. After stirring at room temperature for 1 hr., diethyl ether (20 mL) was added, and the precipitated solid was collected by filtration. The solid was washed twice with ethyl acetate (15 mL) and dried under reduced pressure at 60° C. to give the title compound (1.99 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 2.62(3H,s), 3.32(2H,m), 4.48(2H,t, J=5.0 Hz), 7.07(2H,d, J=8.7 Hz), 8.06(2H,d, J=8.7 Hz), 9.04(2H,bs).

## Reference Example 7

## 2-(Methylamino)ethyl 3-chlorobenzoate hydrochloride



To a mixture of tert-butyl 2-hydroxyethyl (methyl)carbamate (1.75 g) obtained in Reference Example 1 and ethyl acetate (10 mL) were added 3-chlorobenzoyl chloride (1.92 g) and pyridine (0.97 mL). After stirring at room temperature for 1 hr., the mixture was stirred at 60° C. for 6 hrs. Ethyl acetate (80 mL) was added to the reaction mixture, and the mixture was washed with water (20 mL), a saturated aqueous sodium hydrogen carbonate solution (20 mL) and water (20 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, a 4N hydrogen chlo-

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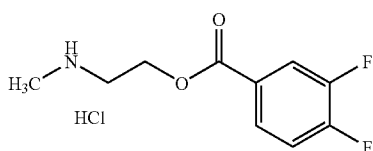
53

ride—ethyl acetate solution (10 mL) was added to the residue. After stirring at room temperature for 22 hrs., diethyl ether (15 mL) was added, and the precipitated solid was collected by filtration. The solid was washed twice with ethyl acetate (15 mL) and dried under reduced pressure at 60° C. to give the title compound (2.01 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 2.63(3H,s), 3.32(2H,m), 4.53(2H,t, J=4.9 Hz), 7.60(1H,t,J=8.0 Hz), 7.78(1H,d,J=8.0 Hz), 8.05(1H,d,J=8.0 Hz), 8.15(1H,s), 9.07(2H,bs).

## Reference Example 8

## 2-(Methylamino)ethyl 3,4-difluorobenzoate hydrochloride

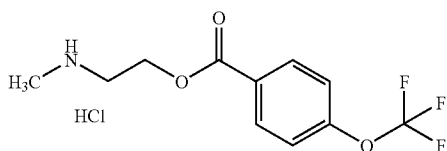


To a mixture of tert-butyl 2-hydroxyethyl(methyl)carbamate (1.75 g) obtained in Reference Example 1 and ethyl acetate (10 mL) were added 3,4-difluorobenzoyl chloride (1.77 g) and pyridine (0.97 mL). After stirring at room temperature for 3 days, ethyl acetate (80 mL) was added to the reaction mixture. The mixture was washed with water (20 mL), a saturated aqueous sodium hydrogen carbonate solution (20 mL) and water (20 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, a 4N hydrogen chloride—ethyl acetate solution (10 mL) was added to the residue. After stirring at room temperature for 4 hrs, the mixture was concentrated under reduced pressure. The residue was washed with ethyl acetate (15 mL), and dried under reduced pressure at 60° C. to give the title compound (2.05 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 2.62(3H,s), 3.32(2H,m), 4.53(2H,t, J=5.0 Hz), 7.64(1H,m), 8.00(1H,m), 8.25(1H,m), 9.25(2H,bs).

## Reference Example 9

## 2-(Methylamino)ethyl 4-trifluoromethoxybenzoate hydrochloride



To a mixture of tert-butyl 2-hydroxyethyl (methyl)carbamate (1.30 g) obtained in Reference Example 1 and ethyl acetate (10 mL) were added 4-trifluoromethoxybenzoyl chloride (1.83 g) and pyridine (0.72 mL). The mixture was stirred at 60° C. for 25 hrs. Ethyl acetate (60 mL) was added to the reaction mixture, and the mixture was washed with water (30 mL), a saturated aqueous sodium hydrogen carbonate solution (20 mL) and water (20 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, a 4N hydrogen chloride—ethyl acetate solution (10 mL)

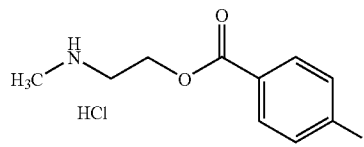
54

was added to the residue. After stirring at room temperature for 14.5 hrs., the mixture was concentrated under reduced pressure. The residue was washed twice with ethyl acetate (15 mL), and dried under reduced pressure at 60° C. to give the title compound (1.83 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 2.63(3H,s), 3.31(2H,m), 4.54(2H,t, J=4.9 Hz), 7.55(2H,d,J=8.5 Hz), 8.24(2H,d,J=8.5 Hz), 9.02(2H,bs).

## Reference Example 10

## 2-(Methylamino)ethyl 4-fluorobenzoate hydrochloride

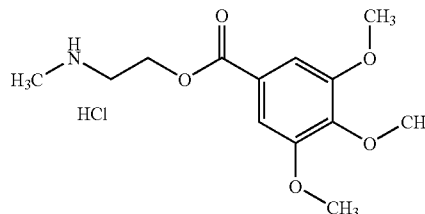


To a mixture of tert-butyl 2-hydroxyethyl (methyl)carbamate (1.75 g) obtained in Reference Example 1 and ethyl acetate (10 mL) were added 4-fluorobenzoyl chloride (1.74 g) and pyridine (0.97 mL). The mixture was stirred at room temperature for 6.5 hrs. Ethyl acetate (80 mL) was added to the reaction mixture, and the mixture was washed with water (30 mL), a saturated aqueous sodium hydrogen carbonate solution (30 mL), water (30 mL) and saturated brine (30 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, a 4N hydrogen chloride—ethyl acetate solution (10 mL) was added to the residue. After stirring at room temperature for 1 hr., the precipitated solid was collected by filtration. The solid was washed twice with ethyl acetate (15 mL) and dried under reduced pressure at 60° C. to give the title compound (1.89 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 2.62(3H,s), 3.32(2H,m), 4.52(2H,t, J=4.9 Hz), 7.34-7.44(2H,m), 8.16-8.24(2H,m), 9.18(2H,bs)

## Reference Example 11

## 2-(Methylamino)ethyl 3,4,5-trimethoxybenzoate hydrochloride



To a mixture of tert-butyl 2-hydroxyethyl (methyl)carbamate (1.75 g) obtained in Reference Example 1 and ethyl acetate (10 mL) were added 3,4,5-trimethoxybenzoyl chloride (2.54 g) and pyridine (0.97 mL). After stirring at 60° C. for 14 hrs., 3,4,5-trimethoxybenzoyl chloride (1.30 g), pyridine (0.97 mL) and ethyl acetate (10 mL) were added, and the mixture was stirred at 60° C. for 24 hrs. The reaction mixture was filtered and ethyl acetate (50 mL) and water (30 mL) were added to the filtrate. After partitioning, ethyl acetate layer was

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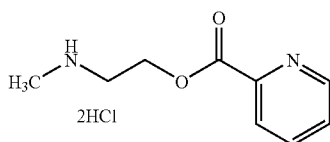
## 55

washed with 1N hydrochloric acid (30 mL), water (30 mL), an aqueous copper (II) sulfate solution (30 mL), water (30 mL) and saturated brine (30 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1). A 4N hydrogen chloride—ethyl acetate solution (10 mL) was added to the purified product. After stirring at room temperature for 4 hrs, the mixture was concentrated under reduced pressure. Toluene (10 mL) was added, and the mixture was concentrated under reduced pressure. The residue was suspended in ethyl acetate, and the solid was filtrated. After washing with ethyl acetate (15 mL), the solid was dried under reduced pressure to give the title compound (1.79 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 2.61(3H,s), 3.28-3.35(2H,m), 3.74(3H,s), 3.87(6H,s), 4.48-4.54(2H,m), 7.40(2H,s), 9.43(2H,br).

## Reference Example 12

## 2-(Methylamino)ethyl 2-pyridinecarboxylate dihydrochloride

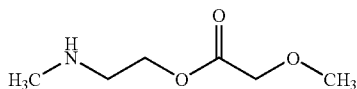


To a solution (100 mL) of tert-butyl 2-hydroxyethyl (methyl)carbamate (1.75 g) obtained in Reference Example 1, 2-pyridinecarbonyl chloride hydrochloride (2.67 g), pyridine (1.21 mL) and 4-dimethylaminopyridine (0.122 g) in tetrahydrofuran was dropwise added triethylamine (2.09 mL) under ice-cooling, and the mixture was stirred at room temperature for 6 hrs. Water (200 mL) was added to the reaction mixture and the mixture was extracted with ethyl acetate (150 mL). The organic layer was washed successively with a 5% aqueous copper (II) sulfate solution (100 mL), water (100 mL) and saturated brine (100 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was dissolved in ethyl acetate (50 mL) and ethanol (100 mL), and a 4N hydrogen chloride—ethyl acetate solution (15 mL) was added. The mixture was stirred at room temperature for 1 hr. The precipitated solid was collected by filtration, washed twice with ethyl acetate (100 mL), and dried under reduced pressure at 60° C. to give the title compound (1.08 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 2.62(3H,t,J=5.4 Hz), 3.35(2H,m), 4.63(2H,t,J=5.0 Hz), 5.26(1H,bs), 7.77-7.84(1H,m), 8.14-8.18(1H,m), 8.36-8.40(1H,m), 8.70-8.90(1H,m), 9.48(2H,br).

## Reference Example 13

## 2-(Methylamino)ethyl methoxyacetate



To a mixture of tert-butyl 2-hydroxyethyl (methyl)carbamate (1.75 g) obtained in Reference Example 1 and ethyl

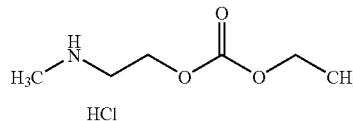
## 56

acetate (10 mL) were added methoxyacetyl chloride (1.20 g) and pyridine (0.97 mL). After stirring at room temperature for 3 hrs., ethyl acetate (70 mL) was added to the reaction mixture. The mixture was washed with water (20 mL), a saturated aqueous sodium hydrogen carbonate solution (20 mL) and water (20 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in ethyl acetate (5 mL), and a 4N hydrogen chloride—ethyl acetate solution (10 mL) was added. After stirring at room temperature for 1 hr., the mixture was concentrated under reduced pressure. Water (60 mL) and diethyl ether (30 mL) were added to the residue. After stirring, the aqueous layer was separated and taken. The aqueous layer was basified with sodium hydrogen carbonate and extracted twice with ethyl acetate (40 mL). The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound (1.00 g) as a colorless oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.40(1H,bs), 3.06(3H,s), 3.44(3H,s), 3.57(2H,t,J=5.1 Hz), 3.75-3.82(2H,m), 4.13(2H,s).

## Reference Example 14

## Ethyl 2-(methylamino)ethyl carbonate hydrochloride

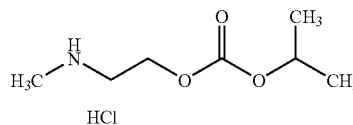


To a mixture of tert-butyl 2-hydroxyethyl (methyl)carbamate (1.75 g) obtained in Reference Example 1 and ethyl acetate (20 mL) were added pyridine (0.97 mL) and 4-dimethylaminopyridine (catalytic amount), and ethyl chlorocarbonate (1.25 mL) was dropwise added. The mixture was stirred overnight at room temperature and ethyl acetate (50 mL) was added. The mixture was washed with water (50 mL), a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, a 4N hydrogen chloride—ethyl acetate solution (10 mL) was added to the residue. After stirring at room temperature for 2 hrs., diethyl ether (10 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (1.66 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.23(3H,t,J=7.1 Hz), 2.54(3H,s), 3.16-3.22(2H,m), 4.15(2H,q,J=7.1 Hz), 4.32-4.37(2H,m), 9.25(2H,br).

## Reference Example 15

## Isopropyl 2-(methylamino)ethyl carbonate hydrochloride



To a mixture of tert-butyl 2-hydroxyethyl (methyl)carbamate (3.50 g) obtained in Reference Example 1 and ethyl



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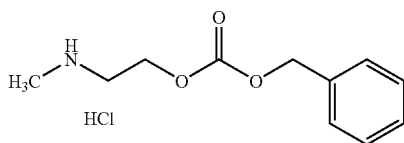
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acetate (20 mL) were added isopropyl chlorocarbonate (1.35 g) and pyridine (1.94 mL) under ice-cooling. After stirring under ice-cooling for 3.5 hrs., isopropyl chlorocarbonate (1.84 g) was added, and the mixture was stirred at room temperature for 2.5 hrs. Ethyl acetate (120 mL) was added to the reaction mixture, and the mixture was washed with water (50 mL) and saturated brine (50 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, a 4N hydrogen chloride—ethyl acetate solution (10 mL) was added to the residue. After stirring at room temperature for 2 hrs., the precipitated solid was collected by filtration. The solid was washed with ethyl acetate (15 mL), and dried under reduced pressure at 60° C. to give the title compound (1.38 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.25(6H,d,J=6.2 Hz), 2.56(3H,s), 3.20(2H,t,J=5.1 Hz), 4.32(2H,t,J=5.1 Hz), 4.80(1H,m), 8.95(2H,bs).

## Reference Example 16

## Benzyl 2-(methylamino)ethyl carbonate hydrochloride

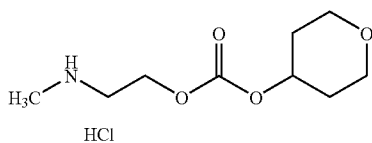


To a mixture of tert-butyl 2-hydroxyethyl (methyl)carbamate (1.75 g) obtained in Reference Example 1 and ethyl acetate (20 mL) were added pyridine (0.97 mL) and 4-dimethylaminopyridine (catalytic amount), and benzyl chlorocarbonate (1.57 mL) was dropwise added. After stirring at room temperature for 2 hrs., pyridine (0.65 mL) and benzyl chlorocarbonate (1.28 mL) were added. After stirring at room temperature for 5 days, pyridine (0.81 mL) was added under ice-cooling and a solution (5 mL) of benzyl chlorocarbonate (1.43 mL) in ethyl acetate was dropwise added slowly. After stirring at room temperature for 2 hrs., ethyl acetate (50 mL) was added to the mixture, washed with water (50 mL), a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, a 4N hydrogen chloride—ethyl acetate solution (10 mL) was added to the residue. After stirring at room temperature for 2 hrs., diethyl ether (10 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (1.99 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 2.55(3H,s), 3.21(2H,t,J=5.1 Hz), 4.37(2H,t,J=5.1 Hz), 5.18(2H,s), 7.30-7.50(5H,m), 9.07(2H,br).

## Reference Example 17

## 2-(Methylamino)ethyl tetrahydropyran-4-yl carbonate hydrochloride



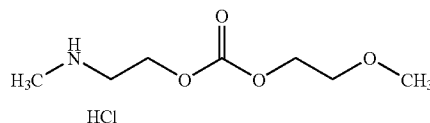
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To a solution (40 mL) of bis(trichloromethyl)carbonate (2.97 g) in tetrahydrofuran was dropwise added a solution (10 mL) of pyridine (2.43 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 10 min., a solution (20 mL) of tetrahydropyran-4-ol (1.91 g) in tetrahydrofuran was dropwise added slowly. After stirring at room temperature for 2 hrs., the mixture was concentrated under reduced pressure, and ethyl acetate (50 mL) and water (50 mL) were added to the residue. The ethyl acetate layer was separated and taken, washed with 0.2N hydrochloric acid (20 mL) and saturated brine (50 mL), and dried over anhydrous magnesium sulfate. Concentration under reduced pressure gave tetrahydropyran-4-yl chlorocarbonate (1.53 g). To a mixture of tert-butyl 2-hydroxyethyl(methyl)carbamate (1.40 g) obtained in Reference Example 1 and tetrahydrofuran (20 mL) was added pyridine (0.78 mL), and a solution (10 mL) of tetrahydropyran-4-yl chlorocarbonate (1.53 g) obtained above in tetrahydrofuran was dropwise added, and the mixture was stirred overnight at room temperature. After concentration of the reaction mixture under reduced pressure, water (50 mL) was added, the mixture was extracted with ethyl acetate (50 mL). The residue was washed with a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=4:1, then 3:2). The obtained colorless oil (2.03 g) was dissolved in diethyl ether (2 mL), and a 4N hydrogen chloride—ethyl acetate solution (5 mL) was added. After stirring at room temperature for 30 min., diethyl ether (10 mL) was added and the mixture was stirred overnight. The precipitated solid was collected by filtration and dried under reduced pressure to give the title compound (1.20 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.50-1.65 (2H,m), 1.87-1.98 (2H,m), 2.54(3H,s), 3.20(2H,m), 3.40-3.50(2H,m), 3.74-3.83 (2H,m), 4.36(2H,t,J=5.1 Hz), 4.72-4.83(1H,m), 9.32(2H,br).

## Reference Example 18

## 2-Methoxyethyl 2-(methylamino)ethyl carbonate hydrochloride



To a mixture of tert-butyl 2-hydroxyethyl (methyl)carbamate (1.75 g) obtained in Reference Example 1 and ethyl acetate (20 mL) was added pyridine (1.62 mL) and a solution (5 mL) of 2-methoxyethyl chlorocarbonate (2.77 g) in ethyl acetate was dropwise added slowly, and the mixture was stirred overnight at room temperature. After concentration of the reaction mixture under reduced pressure, water (50 mL) was added, the mixture was extracted with ethyl acetate (50 mL). The mixture was washed with 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in diethyl ether (2 mL), and a 4N hydrogen chloride—ethyl acetate solution (5 mL) was added. After stirring at room temperature for 30 min., diethyl ether (10 mL) was added, and the mixture was stirred overnight. The precipitated solid was collected by filtration, and dried under reduced pressure to give the title compound (1.56 g) as a white solid.

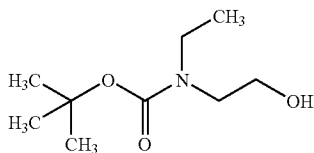
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<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 2.54(3H,s), 3.19(2H,m), 3.26(3H,s), 3.52-3.57(2H,m), 4.20-4.25(2H,m), 4.33-4.39(2H,m), 9.26(2H,br).

## Reference Example 19

## tert-Butyl ethyl(2-hydroxyethyl)carbamate

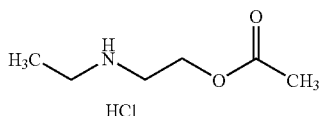


To a mixture of 2-(ethylamino)ethanol (8.91 g) and ethyl acetate (100 mL) was added di-tert-butyl dicarbonate (21.8 g) under ice-cooling. After stirring at room temperature for 3 days, the mixture was washed with saturated brine (100 mL), and dried over anhydrous magnesium sulfate. Concentration under reduced pressure gave the title compound (19.0 g) as a colorless oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.11(3H,t,J=7.0 Hz), 1.47(9H,s), 3.27(2H,q,J=7.0 Hz), 3.37(2H,t,J=5.2 Hz), 3.73(2H,q,J=5.2 Hz).

## Reference Example 20

## 2-(Ethylamino)ethyl acetate hydrochloride



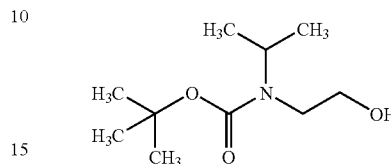
To a mixture of tert-butyl ethyl(2-hydroxyethyl)carbamate (1.89 g) obtained in Reference Example 19 and ethyl acetate (20 mL) were added acetic anhydride (1.04 mL), pyridine (0.89 mL) and 4-dimethylaminopyridine (0.061 g). After stirring at room temperature for 3 hrs., ethyl acetate (50 mL) was added, and the mixture was washed with water (50 mL), a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL). After drying over anhydrous magnesium sulfate, the mixture was concentrated under reduced pressure. A 4N hydrogen chloride—ethyl acetate solution (10 mL) was added to the residue, and the mixture was stirred at room temperature for 1 hr. Ethyl acetate (10 mL) and diethyl ether (20 mL) were added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (1.54 g) as a white solid.

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<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.22(3H,t,J=7.3 Hz), 2.07(3H,s), 2.95(2H,q,J=7.3 Hz), 3.15(2H,t,J=5.3 Hz), 4.24-4.30(2H,m), 9.17(2H,br).

## Reference Example 21

## tert-Butyl 2-hydroxyethyl(isopropyl)carbamate

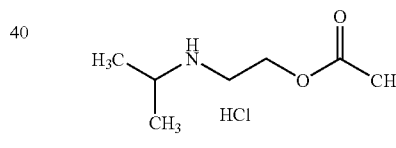


To a solution (30 mL) of 2-(isopropylamino)ethanol (10.0 g) in tetrahydrofuran was added di-tert-butyl dicarbonate (22.2 g), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure and water (100 mL) was added to the residue. The mixture was extracted with ethyl acetate (200 mL). The ethyl acetate layer was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the title compound (21.21 g) as a colorless oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.12(6H,d,J=6.6 Hz), 3.30(2H,t,J=5.0 Hz), 3.71(2H,t,J=5.0 Hz), 3.80-4.30(1H,m).

## Reference Example 22

## 2-(Isopropylamino)ethyl acetate hydrochloride



To a solution (15 mL) of tert-butyl 2-hydroxyethyl (isopropyl)carbamate (5.0 g) obtained in Reference Example 21 in tetrahydrofuran were added pyridine (6.0 mL) and acetic anhydride (2.79 mL) and the mixture was stirred at room temperature for 18 hrs. The reaction mixture was concentrated under reduced pressure, water (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained colorless oil was dissolved in a 4N hydrogen chloride—ethyl acetate solution (10 mL), and the mixture was stirred at room temperature for 1 hr. The precipitated solid was collected by filtration, and dried under reduced pressure to give the title compound (3.14 g) as a colorless solid.

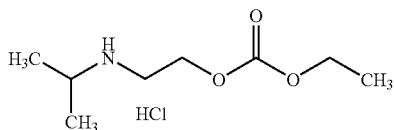
<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.25(6H,d,J=6.6 Hz), 2.08(3H,s), 3.10-3.40(3H,m), 4.29(2H,t,J=6.0 Hz), 9.11(2H,br).

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## Reference Example 23

## Ethyl 2-(isopropylamino)ethyl carbonate hydrochloride

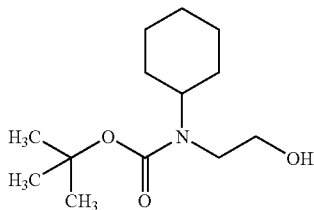


To a solution (15 mL) of tert-butyl 2-hydroxyethyl (isopro-  
pyl)carbamate (5.0 g) obtained in Reference Example 21 in  
tetrahydrofuran were added pyridine (6.0 mL) and ethyl chloro-  
carbonate (2.81 mL) and the mixture was stirred at room  
temperature for 18 hrs. The reaction mixture was concen-  
trated under reduced pressure, and water (50 mL) was added  
to the residue, and the mixture was extracted with ethyl  
acetate (100 mL). The ethyl acetate layer was washed with a  
5% aqueous citric acid solution (50 mL) and saturated brine  
(50 mL), dried over anhydrous sodium sulfate and the mixture  
was concentrated under reduced pressure. The obtained col-  
orless oil was dissolved in a 4N hydrogen chloride—ethyl  
acetate solution (10 mL), and the mixture was stirred at room  
temperature for 1 hr. The precipitated solid was collected by  
filtration and dried under reduced pressure to give the title  
compound (3.34 g) as a colorless solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.20-1.30(9H,m), 3.10-3.40(3H,  
m), 4.17(2H,q,J=7.4 Hz), 4.37(2H,t,J=5.6 Hz), 9.13(2H,br).

## Reference Example 24

## tert-Butyl cyclohexyl(2-hydroxyethyl)carbamate



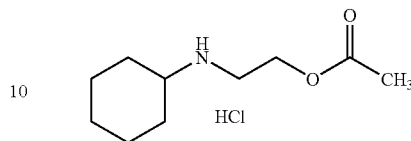
To a solution (200 mL) of 2-(cyclohexylamino)ethanol  
(14.3 g) in ethanol was dropwise added di-tert-butyl dicar-  
bonate (21.8 g). After stirring at room temperature for 2 days,  
the mixture was concentrated under reduced pressure. The  
residue was dissolved in ethyl acetate (200 mL), washed with  
water (100 mL) and saturated brine (100 mL), and dried over  
anhydrous sodium sulfate. Concentration under reduced  
pressure gave the title compound (24.2 g) as a colorless oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.26-1.39(4H,m), 1.47(9H,s), 1.61-  
1.81(6H,m), 3.30-3.40(2H,m), 3.69(2H,t,J=5.4 Hz), 3.66-  
3.90(2H,br).

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## Reference Example 25

## 2-(Cyclohexylamino)ethyl acetate hydrochloride

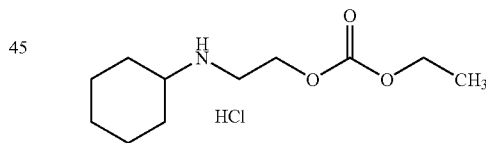


To a solution (50 mL) of tert-butyl cyclohexyl(2-hydroxy-  
ethyl)carbamate (2.43 g) obtained in Reference Example 24  
in tetrahydrofuran were added pyridine (1.05 mL), acetic  
anhydride (1.23 mL) and 4-dimethylaminopyridine (0.122 g)  
under ice-cooling, and the mixture was stirred at room tem-  
perature for 12 hrs. Ethyl acetate (100 mL) was added to the  
reaction mixture and the mixture was washed successively  
with a saturated aqueous sodium hydrogen carbonate solution  
(100 mL), a 5% aqueous copper (II) sulfate solution (100 mL)  
and saturated brine (100 mL), and dried over anhydrous  
sodium sulfate. The mixture was concentrated under reduced  
pressure. The residue was dissolved in ethyl acetate (15 mL),  
and a 4N hydrogen chloride—ethyl acetate solution (15 mL)  
was added. After stirring at room temperature for 3 hrs.,  
diisopropyl ether (20 mL) was added, and the precipitated  
solid was collected by filtration to give the title compound  
(1.78 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.05-2.03(10H,m), 2.07(3H,s),  
2.90-3.10(1H,m), 3.17(2H,t,J=5.2 Hz), 4.29(2H,t,J=5.2 Hz),  
9.19(2H,br).

## Reference Example 26

## 2-(Cyclohexylamino)ethyl ethyl carbonate hydrochloride



To a solution (50 mL) of tert-butyl cyclohexyl(2-hydroxy-  
ethyl)carbamate (2.43 g) obtained in Reference Example 24  
in tetrahydrofuran were added pyridine (1.45 mL), ethyl chloro-  
carbonate (1.71 mL) and 4-dimethylaminopyridine (0.122  
g) under ice-cooling, and the mixture was stirred at room  
temperature for 15 hrs. Ethyl acetate (100 mL) was added to  
the reaction mixture, and the mixture was washed success-  
fully with a saturated aqueous sodium hydrogen carbonate  
solution (100 mL), a 5% aqueous copper (II) sulfate solution  
(100 mL), water (100 mL) and saturated brine (100 mL), and  
dried over anhydrous sodium sulfate. The mixture was con-  
centrated under reduced pressure and the residue was dis-  
solved in ethyl acetate (15 mL). A 4N hydrogen chloride—  
ethyl acetate solution (15 mL) was added. After stirring at  
room temperature for 3 hrs., diisopropyl ether (20 mL) was  
added, and the precipitated solid was collected by filtration to  
give the title compound (2.12 g) as a white solid.

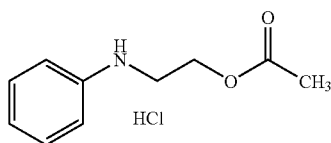
## US 7,790,755 B2

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<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.01-2.08(10H,m), 1.23(3H,t,J=7.0 Hz), 2.90-3.10(1H,m), 3.21(2H,t,J=5.2 Hz), 4.16(2H,q,J=7.0 Hz), 4.39(2H,t,J=5.2 Hz), 9.27(2H,br).

Reference Example 27

2-Anilinoethyl acetate hydrochloride

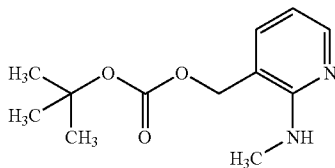


To a solution (700 mL) of 2-anilinoethanol (137 g) in tetrahydrofuran were added pyridine (97.1 mL), acetic anhydride (113.2 mL) and 4-dimethylaminopyridine (12.22 g) under ice-cooling, and the mixture was stirred at room temperature for 20 hrs. Ethyl acetate (1 L) was added to the reaction mixture and the mixture was washed successively with water (1 L), a saturated aqueous sodium hydrogen carbonate solution (1 L), a 5% aqueous copper (II) sulfate solution (1 L) and saturated brine (1 L), dried over anhydrous sodium sulfate, and evaporated under reduced pressure. To a solution of the obtained residue in ethyl acetate (700 mL) was added a 4N hydrogen chloride—ethyl acetate solution (250 mL) under ice-cooling, and the precipitated solid was collected by filtration to give the title compound (156 g) as a white solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD): 2.11(3H,s), 3.71-3.76(2H,m), 4.32-4.37(2H,m), 7.49-7.64(5H,m).

Reference Example 28

tert-Butyl [2-(methylamino)-3-pyridyl]methyl carbonate



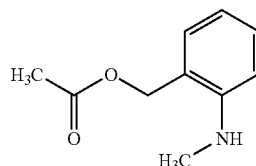
To a solution (50 mL) of [2-(methylamino)-3-pyridyl]methanol (2 g; synthesized according to the method described in WO 01/32652) in tetrahydrofuran were added di-tert-butyl dicarbonate (3.48 g) and 4-dimethylaminopyridine (0.18 g) and the mixture was refluxed for 1 hr. Water (30 mL) was added to the reaction mixture and extracted with ethyl acetate (50 mL). The obtained organic layer was washed with saturated brine (50 mL), and dried over anhydrous sodium sulfate. The residue obtained by concentration under reduced pressure was purified by flash silica gel column chromatography (eluted with ethyl acetate:hexane=1:5) to give the title compound (1.51 g) as a white solid.

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<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.49(9H,s), 3.02(3H,d,J=4.8 Hz), 4.99(2H,s), 5.00(1H,bs), 6.55(1H,dd,J=7.0,5.0 Hz), 7.37(1H,dd,J=7.0,1.8 Hz), 8.16(1H,dd,J=5.0,1.8 Hz).

Reference Example 29

2-(Methylamino)benzyl acetate

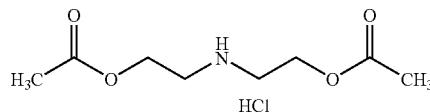


To a solution (50 mL) of [2-(methylamino)phenyl]methanol (1.37 g; synthesized according to the method described in WO 01/32652) in tetrahydrofuran were added pyridine (1.05 mL), acetic anhydride (1.23 mL) and 4-dimethylaminopyridine (0.18 g), and the mixture was stirred at room temperature for 8 hrs. Water (100 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (100 mL). The organic layer was washed successively with a 5% aqueous copper (II) sulfate solution (50 mL), a saturated aqueous sodium hydrogen carbonate solution (50 mL) and saturated brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by flash silica gel column chromatography (eluted with ethyl acetate:hexane=1:5, then 1:3) to give the title compound (0.38 g) as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.08(3H,s), 2.87(3H,s), 4.40(1H,br), 5.08(2H,s), 6.64-6.74(2H,m), 7.17-7.32(2H,m).

Reference Example 30

2-[(2-Acetyloxyethyl)amino]ethyl acetate hydrochloride



To a mixture of 2,2'-iminodiethanol (2.10 g) and ethyl acetate (20 mL) was added di-tert-butyl dicarbonate (4.37 g) under ice-cooling. After stirring for 1.5 hrs. under ice-cooling, acetic anhydride (2.08 mL), pyridine (1.78 mL) and 4-dimethylaminopyridine (0.12 g) were added. After stirring at room temperature for 2 hrs., ethyl acetate (50 mL) was added to the reaction mixture and the mixture was washed with water (50 mL), a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL). After drying over anhydrous magnesium sulfate, the mixture was concentrated under reduced pressure. A 4N hydrogen chloride—ethyl acetate solution (20 mL) was added to the residue, and the mixture was stirred at room temperature for 2 hrs. Diethyl ether (10 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (6.18 g) as a white solid.



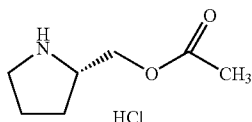
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<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 2.07 (6H,s), 3.23(4H,t,J=5.3 Hz), 4.27-4.33(4H,m), 9.40(2H,br).

## Reference Example 31

## (S)-2-Pyrrolidinylmethyl acetate hydrochloride

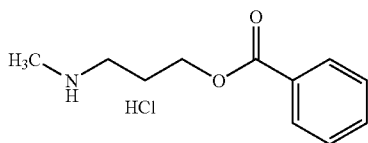


To a mixture of (S)-2-pyrrolidinylmethanol (1.01 g) and ethyl acetate (10 mL) was added di-tert-butyl dicarbonate (2.18 g) under ice-cooling. After stirring for 1 hr. under ice-cooling, acetic anhydride (1.04 mL), pyridine (0.89 mL) and 4-dimethylaminopyridine (0.061 g) were added. After stirring at room temperature for 1 hr., ethyl acetate (50 mL) was added to the reaction mixture, and the mixture was washed with water (50 mL), a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL). After drying over anhydrous magnesium sulfate, the mixture was concentrated under reduced pressure. A 4N hydrogen chloride—ethyl acetate solution (10 mL) was added to the residue, and the mixture was stirred at room temperature for 1 hr. Diethyl ether (10 mL) was added and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (1.68 g) as a pale-brown solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.56-2.10(4H,m), 2.06(3H,s), 3.05-3.24(2H,m), 3.63-3.68(1H,m), 4.15(1H,dd,J=11.8,8.1 Hz), 4.26(1H,dd,J=11.8,4.1 Hz), 9.21(1H,br), 9.87(1H,br).

## Reference Example 32

## 3-(Methylamino)propyl benzoate hydrochloride



To a mixture of 3-amino-1-propanol (0.75 g) and ethyl acetate (2.25 mL) was added a solution (0.25 mL) of di-tert-butyl dicarbonate (2.18 g) in ethyl acetate under ice-cooling. After stirring at room temperature for 21.5 hrs., benzoyl chloride (1.30 mL), pyridine (0.98 mL) and 4-dimethylaminopyridine (0.012 g) were added. After stirring at room temperature for 5 hrs., ethyl acetate (32.5 mL) was added to the reaction mixture, and the mixture was washed with water (12.5 mL) and saturated brine (12.5 mL). After drying over anhydrous magnesium sulfate, the mixture was concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (20 mL), and methyl iodide (5 mL) was added. 60% sodium hydride (0.4 g) was added under ice-cooling. After stirring at room temperature for 3 hrs., the reaction mixture was poured into an ice-cooled aqueous ammonium chloride solution (60 mL). The mixture was extracted with diethyl ether (80 mL) and washed with saturated brine (30 mL). After drying over anhydrous magnesium sulfate, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane=2:1, then ethyl acetate, then

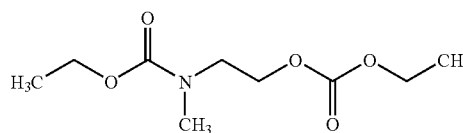
66

acetone:ethyl acetate=1:9) to give 3-[(tert-butoxycarbonyl)(methylamino)propyl benzoate (2.52 g) as a colorless oil. A 4N hydrogen chloride—ethyl acetate solution (10 mL) was added, and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, ethyl acetate (10 mL) was added to the residue and the precipitated solid was collected by filtration. After washing with diethyl ether (10 mL), the solid was dried under reduced pressure to give the title compound (1.73 g) as a colorless solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 2.02-2.16(2H,m), 2.56(3H,s), 3.05(2H,t,J=7.3 Hz), 4.35(2H,t,J=6.1 Hz), 7.51(2H,m), 7.65-7.73(1H,m), 8.01(2H,d,J=7.2 Hz), 8.95(2H,br).

## Reference Example 33

## 2-[(Ethoxycarbonyl)(methylamino)ethyl ethyl carbonate

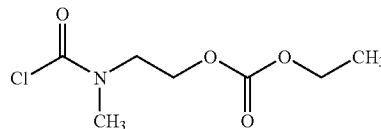


To a solution (1000 mL) of 2-(methylamino)ethanol (100 g) in ethyl acetate was added pyridine (222 mL), ethyl chlorocarbonate (240 mL) was dropwise added over 2 hr. under ice-cooling. After the completion of the dropwise addition, the reaction mixture was stirred at room temperature for 18 hrs. Water (300 mL) was added, and the ethyl acetate layer was separated and washed with 1N hydrochloric acid (200 mL) and saturated brine (200 mL). After drying over anhydrous sodium sulfate, the mixture was concentrated under reduced pressure, and the residue was evaporated under reduced pressure to give the title compound (180 g) as a colorless fraction having a boiling point of 95-100° C. (pressure: 0.1-0.2 mmHg).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.20-1.40(6H,m), 2.97(3H,s), 3.50-3.60(2H,m), 4.05-4.35(6H,m).

## Reference Example 34

## 2-[(Chlorocarbonyl)(methylamino)ethyl ethyl carbonate



To a solution (1500 mL) of 2-[(ethoxycarbonyl)(methylamino)ethyl ethyl carbonate (150 g) obtained in Reference Example 33 in acetonitrile was added phosphorus oxychloride (200 mL), and the mixture was refluxed for 4 days. The reaction mixture was concentrated under reduced pressure and the residue was added to a mixture of water (500 mL)—ice (700 g)—ethyl acetate (300 mL) by portions with stirring. After stirring for 1 min., saturated brine (500 mL) was added, and the mixture was extracted with ethyl acetate (500 mL).

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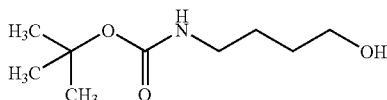
67

The ethyl acetate layer was washed successively with saturated brine (300 mL), a saturated aqueous sodium hydrogen carbonate solution (300 mL) and saturated brine (300 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was evaporated under reduced pressure to give the title compound (77 g) as a colorless fraction having a boiling point of 100-105° C. (pressure: 0.1-0.2 mmHg).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.33(3H,t,J=7.2 Hz), 3.12(3H×0.4,s), 3.22(3H×0.6,s), 3.68(2H×0.6,t,J=4.8 Hz), 3.78(2H×0.4,t,J=4.8 Hz), 4.23(2H,q,J=7.2 Hz), 4.30-4.40(2H,m).

## Reference Example 35

## tert-Butyl 4-hydroxybutylcarbamate

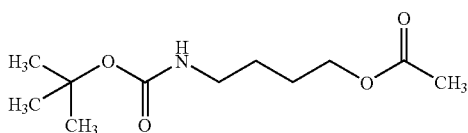


To a mixture of 4-aminobutanol (3.57 g) and ethyl acetate (9 mL) was dropwise added a mixture of di-tert-butyl dicarbonate (8.73 g) and ethyl acetate (1 mL) under ice-cooling. After stirring at room temperature for 24 hrs., the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (200 mL), and the mixture was washed with water (50 mL), 1N hydrochloric acid (40 mL), water (30 mL) and saturated brine (30 mL) and dried over anhydrous magnesium sulfate. Concentration under reduced pressure gave the title compound (7.54 g) as a colorless oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.44(9H,s), 1.47-1.61(4H,m), 3.07-3.22(2H,m), 3.61-3.76(2H,m), 4.62(1H,bs).

## Reference Example 36

## 4-[(tert-Butoxycarbonyl)amino]butyl acetate



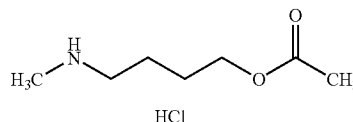
To a mixture of tert-butyl 4-hydroxybutylcarbamate (3.83 g) obtained in Reference Example 35 and ethyl acetate (20 mL) were added pyridine (1.80 mL) and acetic anhydride (2.27 g), and the mixture was stirred at room temperature for 19 hrs. Ethyl acetate (100 mL) was added to the reaction mixture, and the mixture was washed with water (50 mL), an aqueous copper sulfate solution (30 mL), water (30 mL) and saturated brine (30 mL) and dried over anhydrous magnesium sulfate. Concentration under reduced pressure gave the title compound (4.55 g) as a colorless oil.

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<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.44(9H,s), 1.51-1.69(4H,m), 2.05(3H,s), 3.15(2H,m), 4.07(2H,t,J=6.5 Hz), 4.55(1H,bs).

## Reference Example 37

## 4-(Methylamino)butyl acetate hydrochloride

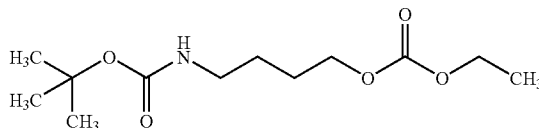


To a solution (20 mL) of 4-[(tert-butoxycarbonyl)amino]butyl acetate (4.50 g) obtained in Reference Example 36 and methyl iodide (4.85 mL) in N,N-dimethylformamide was added sodium hydride (60% in oil, 0.94 g) under ice-cooling. After stirring at room temperature for 4 hrs., the reaction mixture was poured into an ice—aqueous ammonium chloride solution. The mixture was extracted with diethyl ether (120 mL), and the diethyl ether layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:9). To the purified product was added a 4N hydrogen chloride—ethyl acetate solution (20 mL), and the mixture was stirred at room temperature for 2 hrs. Diethyl ether (40 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (2.28 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.58-1.70(4H,m), 2.01(3H,s), 2.50(3H,s), 2.82-2.90(2H,m), 4.00(2H,t,J=6.0 Hz), 8.90(2H,br).

## Reference Example 38

## 4-[(tert-Butoxycarbonyl)amino]butyl ethyl carbonate



To a mixture of tert-butyl 4-hydroxybutylcarbamate (3.71 g) obtained in Reference Example 35 and ethyl acetate (20 mL) were added pyridine (1.71 mL) and ethyl chlorocarbonate (2.55 g) under ice-cooling, and the mixture was stirred at room temperature for 24 hrs. Ethyl acetate (100 mL) was added to the reaction mixture, and the mixture was washed with water (50 mL), an aqueous copper sulfate solution (30 mL), water (30 mL) and saturated brine (30 mL) and dried over anhydrous magnesium sulfate. Concentration under reduced pressure gave the title compound (4.92 g) as a colorless oil.

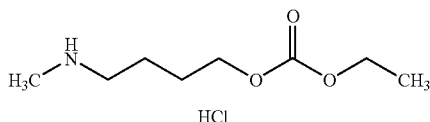
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<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.31(3H,t,J=7.1 Hz), 1.44(9H,s), 1.46-1.80(4H,m), 3.15(2H,m), 4.11-4.25(4H,m), 4.54(1H,bs).

## Reference Example 39

Ethyl 4-(methylamino)butyl carbonate hydrochloride



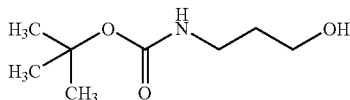
To a solution (20 mL) of 4-[(tert-butoxycarbonyl)amino]butyl ethyl carbonate (4.90 g) obtained in Reference Example 38 and methyl iodide (4.67 mL) in N,N-dimethylformamide was added sodium hydride (60% in oil, 0.90 g) under ice-cooling. After stirring at room temperature for 6 hrs., the reaction mixture was poured into an ice—aqueous ammonium chloride solution, and extracted with diethyl ether (120 mL). The diethyl ether layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:9). To the purified product was added a 4N hydrogen chloride—ethyl acetate solution (20 mL), and the mixture was stirred at room temperature for 2 hrs.

Diethyl ether (40 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (2.86 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.21(3H,t,J=7.1 Hz), 1.51-1.73(4H,m), 2.50(3H,s), 2.82-2.94(2H,m), 4.05-4.15(4H,m), 8.88(2H,br).

## Reference Example 40

tert-Butyl 3-hydroxypropylcarbamate



To a mixture of 3-aminopropanol (7.51 g) and ethyl acetate (30 mL) was dropwise added a mixture of di-tert-butyl dicarbonate (21.8 g) and ethyl acetate (3 mL) under ice-cooling. After stirring at room temperature for 22 hrs., the mixture was concentrated under reduced pressure.

The residue was dissolved in ethyl acetate (200 mL), washed with water (80 mL), 1N hydrochloric acid (60 mL), water (50 mL) and saturated brine (50 mL), and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave the title compound (16.01 g) as a colorless oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.45(9H,s), 1.62-1.70(2H,m), 3.24(2H,q,J=6.6 Hz), 3.66(2H,q,J=5.1 Hz), 4.73(1H,bs).

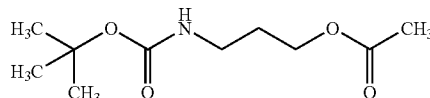
70

## Reference Example 41

3-[(tert-Butoxycarbonyl)amino]propyl acetate

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To a mixture of tert-butyl 3-hydroxypropylcarbamate (8.00 g) obtained in Reference Example 40 and ethyl acetate (50 mL) were added pyridine (4.06 mL) and acetic anhydride (5.13 g), and the mixture was stirred at room temperature for 21 hrs. Ethyl acetate (200 mL) was added to the reaction mixture, and the mixture was washed with water (100 mL), an aqueous copper sulfate solution (40 mL), water (60 mL) and saturated brine (60 mL), and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave the title compound (8.34 g) as a colorless oil.

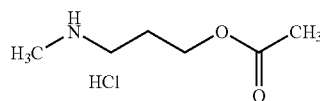
<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.44(9H,s), 1.77-1.86(2H,m), 2.06(3H,s), 3.20(2H,q,J=6.3 Hz), 4.12(2H,t,J=6.3 Hz), 4.67(1H,bs).

## Reference Example 42

3-(Methylamino)propyl acetate hydrochloride

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To a solution (80 mL) of 3-[(tert-butoxycarbonyl)amino]propyl acetate (17.28 g) obtained in Reference Example 41 and methyl iodide (19.8 mL) in N,N-dimethylformamide was added sodium hydride (60% in oil, 3.82 g) under ice-cooling. After stirring at room temperature for 15 hrs., the reaction mixture was poured into an ice—aqueous ammonium chloride solution and extracted with diethyl ether (300 mL). The diethyl ether layer was washed with saturated brine (100 mL), and dried over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:8). To the purified product was added a 4N hydrogen chloride—ethyl acetate solution (40 mL), and the mixture was stirred at room temperature for 2 hrs. Diethyl ether (100 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (2.93 g) as a white solid.

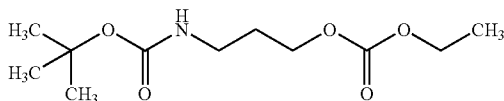
<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.85-1.97(2H,m), 2.02(3H,s), 2.50(3H,s), 2.87-2.96(2H,m), 4.06(2H,t,J=6.3 Hz), 8.87(2H,br).

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Reference Example 43

3-[(tert-Butoxycarbonyl)amino]propyl ethyl carbonate

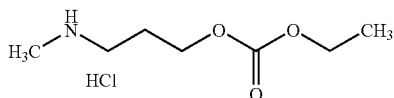


To a mixture of tert-butyl 3-hydroxypropylcarbamate (8.00 g) obtained in Reference Example 40 and ethyl acetate (50 mL) were added pyridine (4.06 mL) and ethyl chlorocarbonate (5.95 g) under ice-cooling, and the mixture was stirred at room temperature for 24 hrs. Ethyl acetate (100 mL) was added to the reaction mixture, and the mixture was washed with water (50 mL), an aqueous copper sulfate solution (30 mL), water (30 mL) and saturated brine (30 mL), and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave the title compound (9.31 g) as a colorless oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.31(3H,t,J=7.1 Hz), 1.44(9H,s), 1.82-1.90(2H,m), 3.22(2H,t,J=6.3 Hz), 4.15-4.23(4H,m), 4.68(1H,bs).

Reference Example 44

Ethyl 3-(methylamino)propyl carbonate hydrochloride



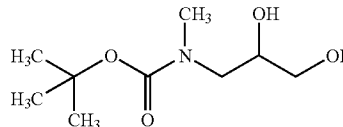
To a solution (40 mL) of 3-[(tert-butoxycarbonyl)amino]propyl ethyl carbonate (9.31 g) obtained in Reference Example 43 and methyl iodide (9.00 mL) in N,N-dimethylformamide was added sodium hydride (60% in oil, 1.82 g) under ice-cooling. After stirring at room temperature for 12 hrs., the reaction mixture was poured into an ice—aqueous ammonium chloride solution and the mixture was extracted with diethyl ether (200 mL). The diethyl ether layer was washed with saturated brine (100 mL), and dried over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:8). To the purified product was added a 4N hydrogen chloride—ethyl acetate solution (40 mL), and the mixture was stirred at room temperature for 2 hrs. Diethyl ether (200 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (4.98 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.21(3H,t,J=7.1 Hz), 1.91-2.00(2H,m), 2.50(3H,s), 2.88-2.98(2H,m), 4.08-4.16(4H,m), 8.90(2H,br).

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Reference Example 45

tert-Butyl (2,3-dihydroxypropyl)methylcarbamate

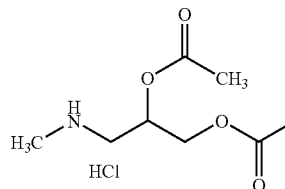


To a mixture of 3-(methylamino)-1,2-propanediol (24.5 g) and ethyl acetate (50 mL) was dropwise added a mixture of di-tert-butyl dicarbonate (51.4 g) and ethyl acetate (10 mL) under ice-cooling. After stirring at room temperature for 15 hrs., the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (150 mL), and the solution was washed with water (80 mL), 1N hydrochloric acid (60 mL), water (50 mL) and saturated brine (50 mL), and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave the title compound (26.9 g) as a colorless oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.47(9H,s), 2.92(3H,s), 3.20-3.36(2H,m), 3.41(2H,bs), 3.50-3.62(2H,m), 3.73-3.88(1H,m).

Reference Example 46

3-(Methylamino)propane-1,2-diyl diacetate hydrochloride



To a mixture of tert-butyl (2,3-dihydroxypropyl)methylcarbamate (10.26 g) obtained in Reference Example 45 and ethyl acetate (50 mL) were added pyridine (10.11 mL) and acetic anhydride (12.76 g), and the mixture was stirred at room temperature for 24 hrs. Ethyl acetate (300 mL) was added to the reaction mixture, and the mixture was washed with water (150 mL), an aqueous copper sulfate solution (100 mL), water (100 mL) and saturated brine (100 mL), and dried over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:8). To the purified product was added a 4N hydrogen chloride—ethyl acetate solution (40 mL), and the mixture was stirred at room temperature for 3 hrs. Diethyl ether (100 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (2.76 g) as a white solid.



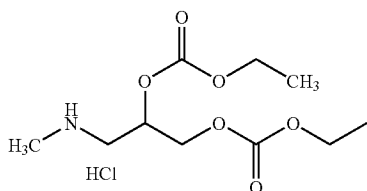
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<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 2.03(3H,s), 2.07(3H,s), 2.55(3H,s), 3.18-3.22(2H,m), 4.09-4.28(2H,m), 5.20-5.27(1H,m), 9.01(2H,br).

## Reference Example 47

Diethyl 3-(methylamino)propane-1,2-diyl  
biscarbonate hydrochloride

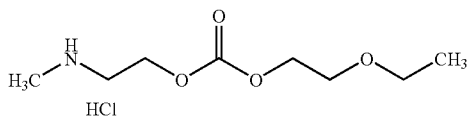


To a mixture of tert-butyl (2,3-dihydroxypropyl)methylcarbamate (15.53 g) obtained in Reference Example 45 and ethyl acetate (100 mL) were added pyridine (18.35 mL) and ethyl chlorocarbonate (24.62 g) under ice-cooling, and the mixture was stirred at room temperature for 96 hrs. Ethyl acetate (300 mL) was added to the reaction mixture, and the mixture was washed with water (150 mL), an aqueous copper sulfate solution (100 mL), water (100 mL) and saturated brine (100 mL), and dried over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:6). To the purified product was added a 4N hydrogen chloride—ethyl acetate solution (80 mL), and the mixture was stirred at room temperature for 3 hrs. Diethyl ether (200 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (5.93 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.20-1.28(6H,m), 2.57(3H,s), 3.12-3.28(2H,m), 4.10-4.43(6H,m), 5.13-5.22(1H,m), 9.14(2H,br).

## Reference Example 48

2-Ethoxyethyl 2-(methylamino)ethyl carbonate  
hydrochloride



To a solution (20 mL) of bis(trichloromethyl)carbonate (2.97 g) in tetrahydrofuran was dropwise added a solution (10 mL) of 2-ethoxyethanol (1.80 g) in tetrahydrofuran under ice-cooling. Then a solution (10 mL) of pyridine (2.43 mL) in tetrahydrofuran was added dropwise, and the mixture was stirred at room temperature for 2 hrs. The reaction mixture was concentrated under reduced pressure and water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with 0.2N hydrochloric acid (20 mL) and saturated brine (50 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give 2-ethoxyethyl chlorocarbonate (1.29 g). A solution (15 mL) of tert-butyl 2-hydroxyethyl(methyl)carbamate (1.23 g) obtained in Reference Example 1 in tetrahydrofuran was added pyridine (0.68 mL),

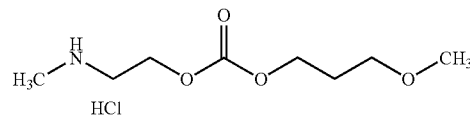
74

and a solution (5 mL) of 2-ethoxyethyl chlorocarbonate obtained above in tetrahydrofuran was dropwise added to the mixture, and the mixture was stirred at room temperature for 3 days. After concentration of the reaction mixture under reduced pressure, water (50 mL) was added thereto and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL), dried over anhydrous magnesium sulfate. The mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:5, then 2:3). The purified product (1.60 g) was dissolved in diethyl ether (3 mL) and a 4N hydrogen chloride—ethyl acetate solution (3 mL) was added. The mixture was stirred overnight at room temperature, and the precipitated solid was collected by filtration and dried under reduced pressure to give the title compound (0.94 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.10(3H,t,J=7.0 Hz), 2.57(3H,s), 3.18-3.25(2H,m), 3.44(2H,q,J=7.0 Hz), 3.56-3.60(2H,m), 4.19-4.24(2H,m), 4.30-4.37(2H,m), 8.79(2H,br).

## Reference Example 49

3-Methoxypropyl 2-(methylamino)ethyl carbonate  
hydrochloride



To a mixture of lithium aluminum hydride (2.85 g) and diethyl ether (100 mL) was dropwise added slowly a solution (50 mL) of methyl 3-methoxypropanoate (11.8 g) in tetrahydrofuran under ice-cooling. After stirring at room temperature for 1 hr., the mixture was again ice-cooled and water (3 mL) and a 10% aqueous sodium hydroxide solution (3 mL) were dropwise added. The mixture was allowed to reach room temperature, and water (9 mL) was dropwise added. The mixture was stirred for a while. The precipitate was filtered off and the filtrate was concentrated under reduced pressure to give 3-methoxypropanol (7.64 g) as a colorless oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.83(2H,quintet,J=5.8 Hz), 2.43(1H,t,J=5.3 Hz), 3.36(3H,s), 3.57(2H,t,J=6.0 Hz), 3.77(2H,q,J=5.5 Hz).

To a solution (50 mL) of bis(trichloromethyl)carbonate (4.45 g) in tetrahydrofuran was dropwise added N-ethyldiisopropylamine (5.75 mL) under ice-cooling. After stirring for a while, a solution (15 mL) of 3-methoxypropanol (2.70 g) obtained above in tetrahydrofuran was dropwise added. The mixture was stirred for 30 min. under ice-cooling and at room temperature for 1 day. After concentration of the reaction mixture under reduced pressure, diluted hydrochloric acid (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with 0.2N hydrochloric acid (30 mL) and saturated brine (30 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 3-methoxypropyl chlorocarbonate (4.39 g). To a solution (20 mL) of tert-butyl 2-hydroxyethyl(methyl)carbamate (1.75 g) obtained in Reference Example 1 in tetrahydrofuran was added pyridine (0.97 mL) and a solution (5 mL) of a 3-methoxypropyl chlorocarbonate (1.83 g) obtained above in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2 hrs. A solution (5 mL) of pyridine (0.65 mL) and 3-methoxypropyl chlorocarbonate

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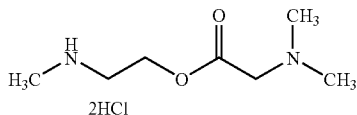
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(1.22 g) in tetrahydrofuran was added and the mixture was further stirred for 1 hr. The reaction mixture was concentrated under reduced pressure and water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (80 mL), and the ethyl acetate layer was washed with a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:9, then 3:7). The purified product (3.40 g) was dissolved in diethyl ether (5 mL) and a 4N hydrogen chloride—ethyl acetate solution (5 mL) was added. The mixture was stirred overnight at room temperature and the reaction mixture was concentrated under reduced pressure. Diethyl ether was added for crystallization to give the title compound (2.06 g) as a colorless solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.78-1.90(2H,m), 2.54(3H,s), 3.15-3.25(2H,m), 3.23(3H,s), 3.33-3.42(2H,m), 4.16(2H,t,J=6.0 Hz), 4.36(2H,t,J=6.0 Hz), 9.27(2H,br).

## Reference Example 50

## 2-(Methylamino)ethyl N,N-dimethylglycinate dihydrochloride

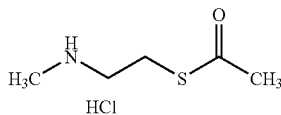


A mixture of tert-butyl 2-hydroxyethyl(methyl)carbamate (3.50 g) obtained in Reference Example 1, N,N-dimethylglycine hydrochloride (5.29 g), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (7.67 g), triethylamine (5.58 mL), 4-dimethylaminopyridine (1.22 g) and N,N-dimethylformamide (50 mL) was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and a saturated aqueous sodium hydrogen carbonate solution (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with methanol:ethyl acetate=5:95, then 20:80). 1N Hydrochloric acid (24 mL) was added to the purified product (2.46 g), and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to give the title compound (2.14 g) as a colorless solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 2.52(3H,s), 2.85(6H,s), 3.20(2H,m), 4.30(2H,s), 4.43-4.49(2H,m), 9.60(2H,br), 10.81(1H,br).

## Reference Example 51

## S-[2-(Methylamino) ethyl]thioacetate hydrochloride



To a solution (50 mL) of tert-butyl 2-hydroxyethyl(methyl)carbamate (3.50 g) obtained in Reference Example 1, thio-

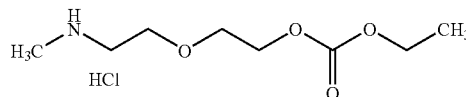
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acetic acid (1.72 mL) and triphenylphosphine (7.87 g) in tetrahydrofuran was dropwise added slowly a solution (10 mL) of diisopropyl azodicarboxylate (5.91 mL) in tetrahydrofuran under ice-cooling. The mixture was stirred under ice-cooling for 1 hr. and at room temperature for 2 hrs. The reaction mixture was again ice-cooled and a solution (10 mL) of triphenylphosphine (7.87 g) and diisopropyl azodicarboxylate (5.91 mL) in tetrahydrofuran was added. The mixture was stirred under ice-cooling for 30 min. Thioacetic acid (1.14 mL) was added and the mixture was stirred under ice-cooling for 30 min. and at room temperature overnight. The reaction mixture was concentrated under reduced pressure and hexane and diisopropyl ether were added to the residue. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. This step was repeated and a saturated aqueous sodium hydrogen carbonate solution (50 mL) was added. The mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=5:95, and then 15:85). A 4N hydrogen chloride—ethyl acetate solution (10 mL) was added to the purified product (4.47 g) and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and ethyl acetate and diethyl ether were added to the residue for crystallization to give the title compound (1.79 g) as a pale-yellow solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 2.38(3H,s), 2.52(3H,s), 2.96-3.08(2H,m), 3.12-3.20(2H,m), 9.35(2H,br).

## Reference Example 52

## Ethyl 2-[2-(methylamino)ethoxy]ethyl carbonate hydrochloride



To a mixture of 2-(2-aminoethoxy)ethanol (99.52 g) and ethyl acetate (200 mL) was dropwise added a mixture of di-tert-butyl dicarbonate (208.57 g) and ethyl acetate (50 mL) under ice-cooling. After stirring at room temperature for 60 hrs., the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (500 mL), washed with water (200 mL), 1N hydrochloric acid (200 mL), water (300 mL) and saturated brine (300 mL), and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave tert-butyl [2-(2-hydroxyethoxy)ethyl]carbamate (169.2 g) as a colorless oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.45(9H,s), 3.33(2H,q,J=5.1 Hz), 3.54-3.59(4H,m), 3.74(2H,q,J=5.1 Hz), 4.88(2H,bs).

To a mixture of tert-butyl [2-(2-hydroxyethoxy)ethyl]carbamate (53.93 g) obtained above and ethyl acetate (350 mL) were added pyridine (53.78 mL) and ethyl chlorocarbonate (70.57 g) under ice-cooling, and the mixture was stirred at room temperature for 96 hrs. Ethyl acetate (500 mL) was added to the reaction mixture, and the mixture was washed with water (500 mL), an aqueous copper sulfate solution (200 mL), water (300 mL) and saturated brine (300 mL) and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave 2-[2-[(tert-butoxycarbonyl)amino]ethoxy]ethyl ethyl carbonate (93.19 g) as a colorless oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.32(3H,t,J=7.2 Hz), 1.44(9H,s), 3.32(2H,t, J=5.1 Hz), 3.54(2H,t, J=5.1 Hz), 3.67-3.74(2H,m), 4.21(2H,q, J=7.2 Hz), 4.26-4.31(2H,m), 4.91(1H,bs).

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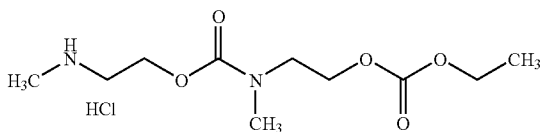
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To a solution (350 mL) of 2-[2-[(tert-butoxycarbonyl)amino]ethoxy]ethyl ethyl carbonate (93.15 g) obtained above and methyl iodide (83.6 mL) in N,N-dimethylformamide was added sodium hydride (60% in oil, 16.12 g) under ice-cooling. After stirring at room temperature for 24 hrs., the reaction mixture was poured into an ice—aqueous ammonium chloride solution, and extracted with diethyl ether (800 mL). The diethyl ether layer was washed with saturated brine (300 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:8). To the purified product was added a 4N hydrogen chloride—ethyl acetate solution (300 mL) was added, and the mixture was stirred at room temperature for 2 hrs. Diethyl ether (300 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (33.21 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.21(3H,t,J=7.2 Hz), 2.51(3H,s), 3.02-3.09(2H,m), 3.65-3.72(4H,m), 4.12(2H,q,J=7.2 Hz), 4.22(2H,t,J=4.5 Hz), 9.06(2H,br).

## Reference Example 53

Ethyl 2-[methyl[[2-(methylamino)ethoxy]carbonyl]amino]ethyl carbonate hydrochloride



To a solution (100 mL) of bis(trichloromethyl)carbonate (11.87 g) in tetrahydrofuran was dropwise added a solution (20 mL) of pyridine (9.71 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., a solution (20 mL) of tert-butyl 2-hydroxyethyl(methyl)carbamate (17.52 g) obtained in Reference Example 1 in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 15 hrs. After concentration under reduced pressure, water (500 mL) and anhydrous sodium sulfate were added to the residue. After filtration, the filtrate was concentrated under reduced pressure. To the obtained residue were added a solution (50 mL) of 2-(methylamino)ethanol (5.00 g) in ethyl acetate and triethylamine (10.0 mL) under ice-cooling and the mixture was stirred at room temperature for 15 hrs. Ethyl acetate (300 mL) was added to the reaction mixture, washed with water (150 mL) and saturated brine (200 mL) and dried over anhydrous sodium sulfate. After concentration under reduced pressure, to a mixture of the residue and ethyl acetate (100 mL) were added pyridine (2.91 mL) and ethyl chlorocarbonate (3.44 g) under ice-cooling, and the mixture was stirred at room temperature for 48 hrs. Ethyl acetate (200 mL) was added to the reaction mixture, washed with water (100 mL), an aqueous copper sulfate solution (50 mL), water (50 mL) and saturated brine (50 mL), and dried over anhydrous sodium sulfate. The mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:3). To the purified product was added a 4N hydrogen chloride—ethyl acetate solution (30 mL), and the mixture was stirred at room temperature for 3 hrs. Diethyl ether (100 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (2.90 g) as a white solid.

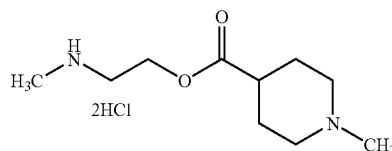
<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.21(3H,t,J=7.2 Hz), 2.57(3H,bs), 2.86(1.5H,s), 2.93(1.5H,s), 3.16(2H,bs), 3.34(1H,bs), 3.48

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(1H,t,J=5.1 Hz), 3.58(1H,t,J=5.1 Hz), 4.12(2H,q,J=7.2 Hz), 4.16-4.24(4H,m), 8.94(1H,br).

## Reference Example 54

2-(Methylamino)ethyl  
1-methylpiperidine-4-carboxylate dihydrochloride



A mixture of ethyl piperidine-4-carboxylate (4.72 g), methyl iodide (2.24 mL), potassium carbonate (8.29 g) and acetonitrile (50 mL) was stirred at room temperature for 2 hrs. The reaction mixture was concentrated under reduced pressure and water (150 mL) was added. The mixture was extracted with ethyl acetate (150 mL). The ethyl acetate layer was washed with saturated brine (100 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. A 1N aqueous sodium hydroxide solution (20 mL) was added to the residue (2.64 g), and the mixture was stirred overnight at room temperature. The reaction mixture was neutralized by adding 1N hydrochloric acid (20 mL) and the mixture was concentrated under reduced pressure. Ethanol was added to the residue, and the precipitate was filtered off. The filtrate was concentrated under reduced pressure. This step was repeated and ethanol and ethyl acetate were added to the residue for crystallization to give 1-methylpiperidine-4-carboxylic acid (1.79 g) as a colorless solid.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD): 1.80-1.98(2H,m), 2.00-2.14(2H,m), 2.28-2.42(1H,m), 2.78(3H,s), 2.88-3.04(2H,m), 3.32-3.44(2H,m).

A mixture of 1-methylpiperidine-4-carboxylic acid (1.72 g) obtained above, tert-butyl 2-hydroxyethyl(methyl)carbamate (1.75 g) obtained in Reference Example 1, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (2.30 g), 4-dimethylaminopyridine (0.24 g) and acetonitrile (50 mL) was stirred at room temperature for 16 hrs. The reaction mixture was concentrated under reduced pressure and a saturated aqueous sodium hydrogen carbonate solution (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=50:50, then 80:20). 1N Hydrochloric acid (25 mL) was added to the purified product (2.73 g), and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and isopropanol was added. The mixture was again concentrated under reduced pressure and the precipitated solid was collected by filtration to give the title compound (1.72 g) as a colorless solid.

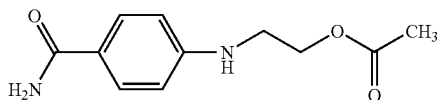
<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.70-2.20(4H,m), 2.40-3.50(13H,m), 4.31(2H,m), 9.25(2H,br), 10.77(1H,br).

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## Reference Example 55

2-[[4-(Aminocarbonyl)phenyl]amino]ethyl acetate



A mixture of 4-fluorobenzonitrile (6.06 g), 2-aminoethanol (3.71 g), potassium carbonate (8.29 g) and dimethyl sulfoxide (50 mL) was stirred at 100° C. overnight. Water (200 mL) was added to the reaction mixture and the mixture was extracted with ethyl acetate (200 mL×4). The ethyl acetate layer was washed with saturated brine (100 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=30:70, then 50:50, then 80:20, then ethyl acetate) to give 4-[(2-hydroxyethyl)amino]benzonitrile (5.89 g) as a yellow solid.

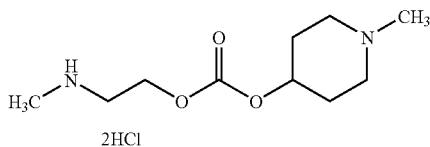
<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.04(1H,t,J=4.8 Hz), 3.33(2H,m), 3.86(2H,q,J=4.8 Hz), 4.66(1H,br), 6.58(2H,d,J=8.7 Hz), 7.39(2H,d,J=8.7 Hz).

A mixture of 4-[(2-hydroxyethyl)amino]benzonitrile (0.81 g) obtained above, potassium hydroxide (1.12 g) and tert-butanol (20 mL) was stirred at 100° C. for 1 hr. Water (100 mL) was added to the reaction mixture, and extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (80 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. To a solution (10 mL) of the residue (0.83 g), pyridine (0.49 mL) and 4-dimethylaminopyridine (0.061 g) in tetrahydrofuran was dropwise added a solution (1 mL) of acetic anhydride (0.57 mL) in tetrahydrofuran. The mixture was stirred at room temperature for 1 hr., water (80 mL) was added, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (80 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=30:70, then 60:40) to give the title compound (0.68 g) as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.08(3H,s), 3.44(2H,q,J=5.6 Hz), 4.29(2H,t,J=5.4 Hz), 4.48(1H,br), 6.59(2H,d,J=8.9 Hz), 7.43(2H,d,J=8.9 Hz).

## Reference Example 56

2-(Methylamino)ethyl 1-methyl-4-piperidinyl carbonate dihydrochloride



To a solution (40 mL) of N,N'-carbonyldiimidazole (3.36 g) in tetrahydrofuran was dropwise added slowly a solution (10 mL) of tert-butyl 2-hydroxyethyl(methyl)carbamate (3.30 g) obtained in Reference Example 1 in tetrahydrofuran under ice-cooling. The mixture was stirred under ice-cooling for 40 min. and at room temperature for 2 hrs. N,N'-Carbon-

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ylidiimidazole (0.31 g) was added and the mixture was further stirred for 3 days. The reaction mixture was concentrated under reduced pressure and ethyl acetate (150 mL) was added to the residue. The mixture was washed with saturated brine (100 mL×2), water (50 mL×3) and saturated brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 2-[(tert-butoxycarbonyl)(methylamino)ethyl 1H-imidazole-1-carboxylate (5.24 g) as a colorless oil.

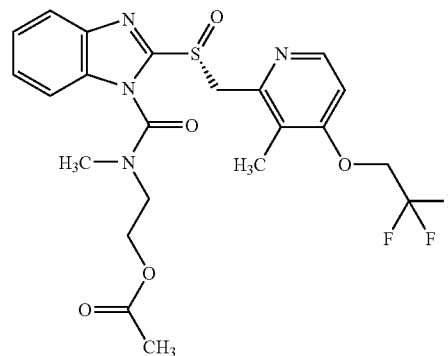
<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.39(9H×0.5,s), 1.42(9H×0.5,s), 2.94(3H,m), 3.63(2H,m), 4.51(2H,t,J=5.3 Hz), 7.06(1H,m), 7.42(1H,m), 8.13(1H,s).

A mixture of 2-[(tert-butoxycarbonyl)(methylamino)ethyl 1H-imidazole-1-carboxylate (1.35 g) obtained above, 1-methyl-4-piperidinol (1.38 g) and acetonitrile (20 mL) was stirred overnight at room temperature. 1-Methyl-4-piperidinol (0.92 g) was added and the mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure and a saturated aqueous sodium hydrogen carbonate solution (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. 1N Hydrochloric acid (12 mL) was added to the residue (1.60 g), and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, water, isopropanol and ethyl acetate were added, and the precipitated solid was collected by filtration to give the title compound (1.09 g) as a colorless solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.85-2.20(4H,m), 2.55(3H,s), 2.70(3H×0.5,s), 2.73(3H×0.5,s), 2.90-3.50(6H,m), 4.38(2H,m), 4.65-5.00(1H,m), 9.21(2H,br), 11.10(1H,br).

## Synthetic Example 1

2-[Methyl][(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate



To a solution (30 mL) of bis(trichloromethyl)carbonate (0.50 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl acetate hydrochloride (0.77 g) obtained in Reference Example 2 was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The mixture was concentrated under reduced pressure.



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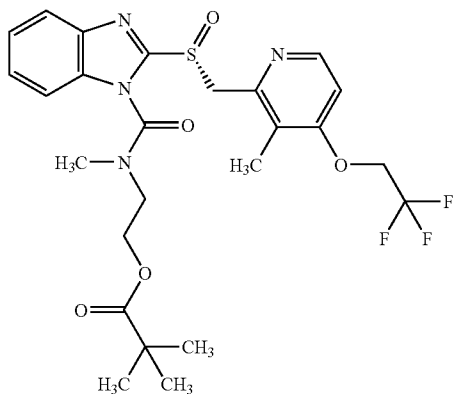
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sure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.84 mL) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60° C. overnight. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate), and further by silica gel column chromatography (eluted with ethyl acetate:hexane=2:1, then ethyl acetate, then acetone:ethyl acetate=1:4, then 1:1) to give the title compound (1.13 g) as a yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.10(3H,s), 2.24(3H,s), 3.09(3H,bs), 3.60-4.00(2H,br), 4.25-4.50(4H,m), 4.89(1H,d,J=13.3 Hz), 5.05(1H,d,J=13.3 Hz), 6.65(1H,d,J=5.5 Hz), 7.35-7.51(3H,m), 7.80-7.90(1H,m), 8.35(1H,d,J=5.5 Hz).

## Synthetic Example 2

2-[Methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl trimethylacetate



To a solution (30 mL) of bis(trichloromethyl)carbonate (0.50 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., 2-(methylamino)ethyl trimethylacetate hydrochloride (0.98 g) obtained in Reference Example 3 was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred overnight at room temperature. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL), and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.84 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred overnight at 60° C. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by flash silica gel

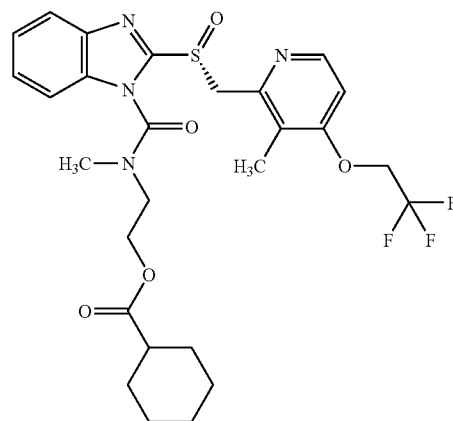
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column chromatography (eluted with acetone:hexane=1:3, then 3:2). Crystallization from acetone-diisopropyl ether and recrystallization from acetone-diisopropyl ether gave the title compound (1.01 g) as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.23(9H,s), 2.23(3H,s), 3.08(3H,bs), 3.40-4.30(2H,br), 4.30-4.50(4H,m), 4.80-5.20(2H,br), 6.64(1H,d,J=5.7 Hz), 7.35-7.50(3H,m), 7.78-7.88(1H,m), 8.35(1H,d,J=5.7 Hz).

## Synthetic Example 3

2-[Methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl cyclohexanecarboxylate



To a solution (30 mL) of bis(trichloromethyl)carbonate (0.50 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl cyclohexanecarboxylate hydrochloride (1.11 g) obtained in Reference Example 4 was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.84 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred overnight at 60° C. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by flash silica gel

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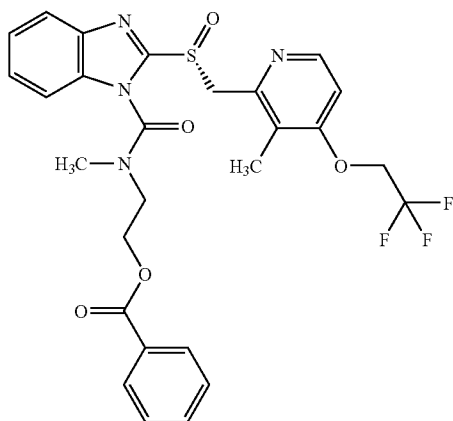
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column chromatography (eluted with acetone:hexane=1:3, then 3:2). Crystallization from acetone-diisopropyl ether and recrystallization from acetone-diisopropyl ether gave the title compound (1.11 g) as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.10-1.55(5H,m), 1.55-1.82(3H,m), 1.84-1.98(2H,m), 2.23(3H,s), 2.27-2.40(1H,m), 3.08(3H,bs), 3.40-4.30(2H,br), 4.30-4.50(4H,m), 4.80-5.15(2H,br), 6.64 (1H,d,J=5.4 Hz), 7.35-7.48(3H,m), 7.84(1H,d,J=6.9 Hz), 8.34 (1H,d,J=5.4 Hz)

## Synthetic Example 4

2-[Methyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl benzoate



To a solution (30 mL) of bis(trichloromethyl)carbonate (0.50 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., 2-(methylamino)ethyl benzoate hydrochloride (1.08 g) obtained in Reference Example 5 was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred overnight at room temperature. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.84 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred overnight at 60° C. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by flash silica gel column chromatography (eluted with acetone:hexane=1:3, then 3:2). Crystallization from acetone-diethyl ether and recrystallization from acetone-diethyl ether gave the title compound (1.09 g) as a colorless solid.

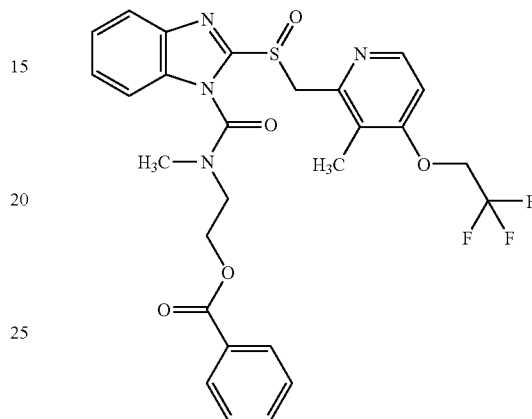
<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.22(3H,s), 3.12(3H,bs), 3.50-4.30 (2H,br), 4.37(2H,q,J=7.8 Hz), 4.68(2H,m), 4.80-5.20(2H,

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br), 6.63(1H,d,J=5.7 Hz), 7.26-7.48(5H,m), 7.53-7.61(1H,m), 7.82(1H,d,J=8.1 Hz), 8.04(2H,d,J=7.2 Hz), 8.33(1H,d,J=5.7 Hz).

## Synthetic Example 5

2-[Methyl[[[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl benzoate



To a solution (30 mL) of bis(trichloromethyl)carbonate (0.99 g) in tetrahydrofuran was dropwise added a solution (2 mL) of pyridine (0.81 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl benzoate hydrochloride (2.16 g) obtained in Reference Example 5 was added. After addition of a solution (2 mL) of triethylamine (1.39 mL) in tetrahydrofuran, the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, ethyl acetate (100 mL) and water (100 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (40 mL). 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (2.90 g), triethylamine (2.20 mL) and 4-dimethylaminopyridine (0.096 g) were added, and the mixture was stirred at 60° C. for 2 hr. After concentration under reduced pressure, ethyl acetate (150 mL) and water (80 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate). Recrystallization from acetone gave the title compound (2.62 g) as a colorless solid.

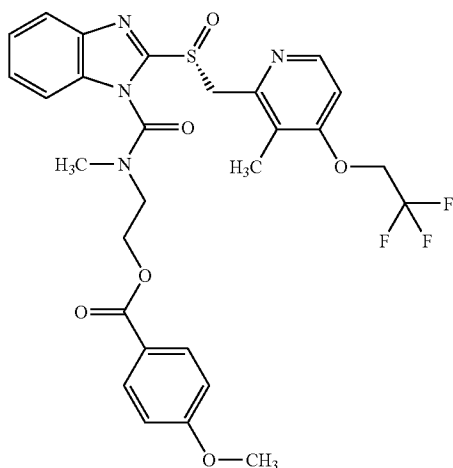
<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.22(3H,s), 3.13(3H,bs), 3.68-3.98 (2H,bm), 4.38(2H,q,J=7.8 Hz), 4.69(2H,m), 4.80-5.10(2H,bm), 6.64(1H,d,J=5.7 Hz), 7.27-7.48(5H,m), 7.59(1H,m), 7.83(1H,m), 8.06(2H,d,J=6.0 Hz), 8.35(1H,d,J=5.7 Hz).

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Synthetic Example 6

2-[Methyl[[[R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl 4-methoxybenzoate



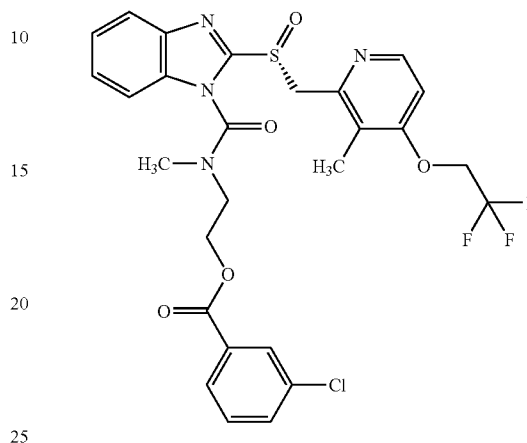
To a solution (18 mL) of bis(trichloromethyl)carbonate (0.584 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 40 min., 2-(methylamino)ethyl 4-methoxybenzoate hydrochloride (1.48 g) obtained in Reference Example 6 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was added and the mixture was stirred at room temperature for 80 min. After concentration under reduced pressure, ethyl acetate (80 mL) and water (50 mL) were added to the residue and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (25 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.55 g), triethylamine (1.17 mL) and 4-dimethylaminopyridine (0.051 g) were added, and the mixture was stirred at 60° C. for 3 hrs. After concentration under reduced pressure, ethyl acetate (150 mL) and water (50 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate). Recrystallization from ethyl acetate-hexane gave the title compound (1.08 g) as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.22(3H,s), 3.11(3H,bs), 3.68-3.90 (2H,bm), 3.85(3H,s), 4.37(2H,q,J=7.9 Hz), 4.58-4.72(2H,m), 4.82-5.14(2H,bm), 6.63(1H,d,J=5.7 Hz), 6.91(2H,d,J=9.0 Hz), 7.27-7.40(3H,m), 7.82(1H,m), 7.99(2H,d,J=9.0 Hz), 8.33(1H,d,J=5.7 Hz).

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Synthetic Example 7

2-[Methyl[[[R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl 3-chlorobenzoate



To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl 3-chlorobenzoate hydrochloride (1.50 g) obtained in Reference Example 7 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was added and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, ethyl acetate (80 mL) and water (40 mL) were added to the residue and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (25 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.44 g), triethylamine (1.09 mL) and 4-dimethylaminopyridine (0.048 g) were added, and the mixture was stirred at 60° C. for 3 hrs. After concentration under reduced pressure, ethyl acetate (80 mL) and water (40 mL) were added to the residue and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (0.84 g) as colorless syrup.

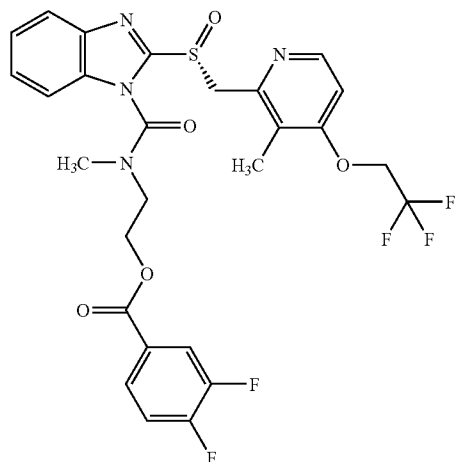
<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.21(3H,s), 3.12(3H,bs), 3.78-4.08 (2H,bm), 4.38(2H,q,J=7.8 Hz), 4.64-5.08(4H,bm), 6.64(1H,d,J=5.2 Hz), 7.34-7.42(4H,m), 7.56(1H,m), 7.82(1H,m), 7.94(1H,d,J=7.6 Hz), 8.02(1H,s), 8.34(1H,d,J=5.2 Hz).

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## Synthetic Example 8

2-[Methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl 3,4-difluorobenzoate



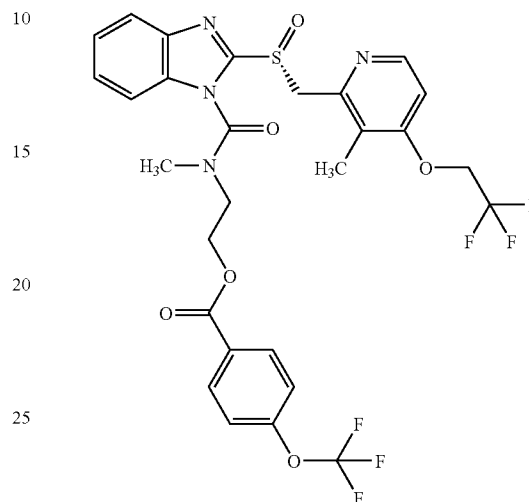
To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl 3,4-difluorobenzoate hydrochloride (1.51 g) obtained in Reference Example 8 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was added and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, ethyl acetate (80 mL) and water (50 mL) were added to the residue and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (25 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.71 g), triethylamine (1.29 mL) and 4-dimethylaminopyridine (0.056 g) were added, and the mixture was stirred at 60° C. for 17 hrs. After concentration under reduced pressure, ethyl acetate (100 mL) and water (50 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, and the aqueous layer was extracted with ethyl acetate (20 mL). Ethyl acetate layers were combined, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then 2:1), and by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1). Crystallization from acetone-diisopropyl ether and recrystallization from ethyl acetate-hexane gave the title compound (1.37 g) as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.21(3H,s), 3.11(3H,bs), 3.82-4.08 (2H,bm), 4.38(2H,q,J=7.8 Hz), 4.60-5.14(4H,bm), 6.63(1H, d,J=5.7 Hz), 7.20(1H,m), 7.33-7.41(3H,m), 7.78-7.92(3H, m), 8.33(1H,d,J=5.7 Hz).

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## Synthetic Example 9

2-[Methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl 4-trifluoromethoxybenzoate



To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl 4-trifluoromethoxybenzoate hydrochloride (1.79 g) obtained in Reference Example 9 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was added and the mixture was stirred at room temperature for 1.5 hrs. After concentration under reduced pressure, ethyl acetate (80 mL) and water (50 mL) were added to the residue and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (25 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.57 g), triethylamine (1.18 mL) and 4-dimethylaminopyridine (0.052 g) were added, and the mixture was stirred at 60° C. for 4.5 hrs. After concentration under reduced pressure, ethyl acetate (100 mL) and water (50 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, and the aqueous layer was extracted with ethyl acetate (30 mL). The ethyl acetate layers were combined, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1), and further by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1) to give the title compound (1.44 g) as colorless syrup.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.22(3H,s), 3.11(3H,bs), 3.85-4.05 (2H,bm), 4.38(2H,q,J=7.8 Hz), 4.60-5.12(4H,bm), 6.64(1H, d,J=5.7 Hz), 7.24(2H,d,J=8.7 Hz), 7.25-7.40(3H,m), 7.82 (1H,d,J=7.2 Hz), 8.09(2H,d,J=8.7 Hz), 8.33(1H,d,J=5.7 Hz).

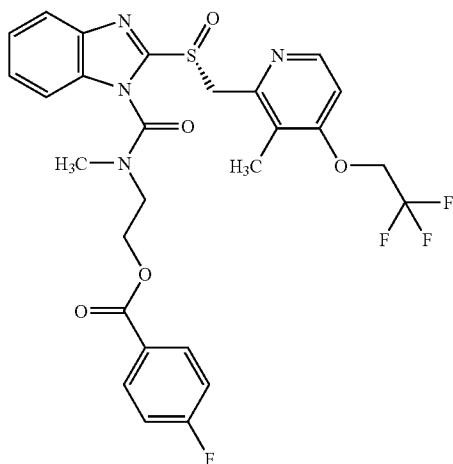


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Synthetic Example 10

2-[Methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl 4-fluorobenzoate



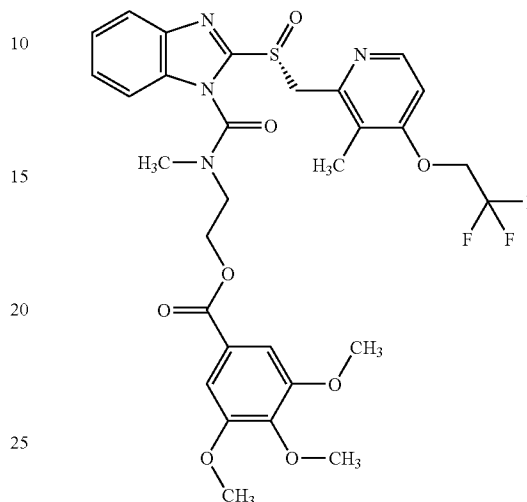
To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl 4-fluorobenzoate hydrochloride (1.40 g) obtained in Reference Example 10 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was added and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, ethyl acetate (80 mL) and water (40 mL) were added to the residue and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.32 g), triethylamine (1.00 mL) and 4-dimethylaminopyridine (0.049 g) were added, and the mixture was stirred at 60° C. for 14.5 hrs. After concentration under reduced pressure, ethyl acetate (150 mL) and water (50 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was crystallized from ethyl acetate:hexane=1:1 and collected by filtration. Recrystallization from acetone gave the title compound (1.39 g) as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.22(3H,s), 3.12(3H,bs), 3.78-4.20 (2H,bm), 4.38(2H,q,J=7.8 Hz), 4.58-5.08(4H,bm), 6.65(1H, d,J=5.6 Hz), 7.11(2H,t,J=8.4 Hz), 7.28-7.44(3H,m), 7.81-7.86(1H,m), 8.03-8.11(2H,m), 8.35(1H,d,J=5.6 Hz).

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Synthetic Example 11

2-[Methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl 3,4,5-trimethoxybenzoate



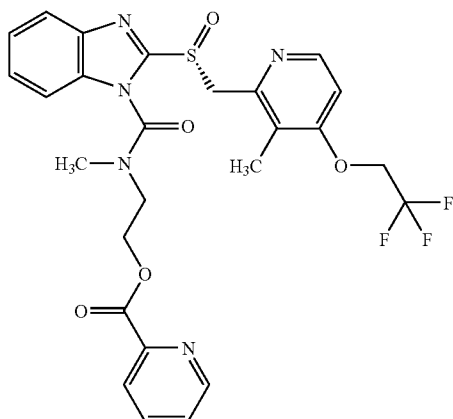
To a solution (30 mL) of bis(trichloromethyl)carbonate (0.60 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 10 min., 2-(methylamino)ethyl 3,4,5-trimethoxybenzoate hydrochloride (1.22 g) obtained in Reference Example 11 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with dilute hydrochloric acid (20 mL) and saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.84 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred at 60° C. for 3 hrs. and at room temperature for 2 days. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by flash silica gel column chromatography (eluted with acetone: hexane=1:3, then 3:2) to give the title compound (1.56 g) as a yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.21(3H,s), 3.12(3H,bs), 3.50-4.30 (2H,br), 3.83(6H,s), 3.90(3H,s), 4.38(2H,q,J=7.8 Hz), 4.67 (2H,m), 4.80-5.15(2H,br), 6.64(1H,d,J=5.7 Hz), 7.25-7.40 (5H,m), 7.78-7.86(1H,m), 8.33(1H,d,J=5.7 Hz).

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Synthetic Example 12  
2-[Methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl 2-pyridinecarboxylate

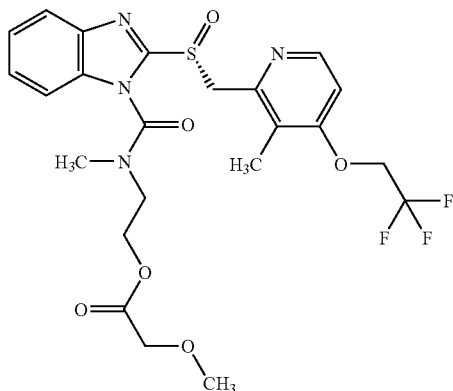


To a solution (30 mL) of bis(trichloromethyl)carbonate (0.422 g) in tetrahydrofuran was dropwise added pyridine (0.345 mL) under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl 2-pyridinecarboxylate dihydrochloride (1.08 g) obtained in Reference Example 12 was added. After dropwise addition of triethylamine (1.19 mL), the mixture was stirred at room temperature for 2 hrs. The precipitated solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (10 mL), and (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.31 g), triethylamine (0.99 mL) and 4-dimethylaminopyridine (0.043 g) were added. The mixture was stirred at 60° C. for 24 hrs. Ethyl acetate (100 mL) was added to the reaction mixture, and the mixture was washed with water (100 mL) and saturated brine (100 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=4:1). Crystallization from acetone-diethyl ether gave the title compound (0.9 g) as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.22(3H,s), 3.16(3H,s), 3.80-4.20(2H,m), 4.38(2H,q,J=7.8 Hz), 4.60-5.10(4H,m), 6.64(1H,d,J=5.8 Hz), 7.29-7.40(2H,m), 7.47-7.52(2H,m), 7.81-7.89(2H,m), 8.14(1H,d,J=7.8 Hz), 8.34(1H,d,J=5.8 Hz), 8.75-8.79(1H,m).

## Synthetic Example 13

2-[Methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl methoxyacetate



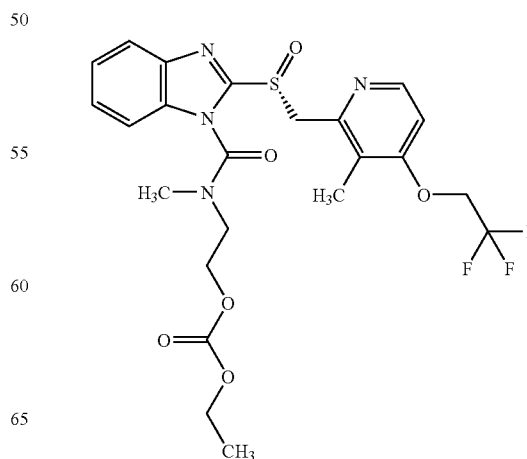
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To a solution (15 mL) of bis(trichloromethyl)carbonate (0.652 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.55 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl methoxyacetate (0.99 g) obtained in Reference Example 13 was added. The mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, ethyl acetate (80 mL) and water (50 mL) were added to the residue and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (15 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.13 g), triethylamine (0.86 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred at 60° C. for 4 days. After concentration under reduced pressure, ethyl acetate (80 mL) and water (30 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, and the ethyl acetate layer was washed with a saturated aqueous sodium hydrogen carbonate solution (30 mL) and water (30 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate, then acetone:ethyl acetate=1:3), and further by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then 3:1) to give the title compound (0.588 g) as colorless syrup.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.32(3H,s), 2.68(3H,s), 3.48(3H,s), 3.69-4.02(4H,m), 4.38(2H,q,J=7.8 Hz), 4.67(2H,t,J=6.6 Hz), 4.99(1H,d,J=13.9 Hz), 5.12(1H,d,J=13.9 Hz), 6.63(1H,d,J=5.7 Hz), 7.29-7.46(2H,m), 7.62(1H,m), 7.81(1H,m), 8.25(1H,d,J=5.7 Hz).

## Synthetic Example 14

Ethyl 2-[methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate



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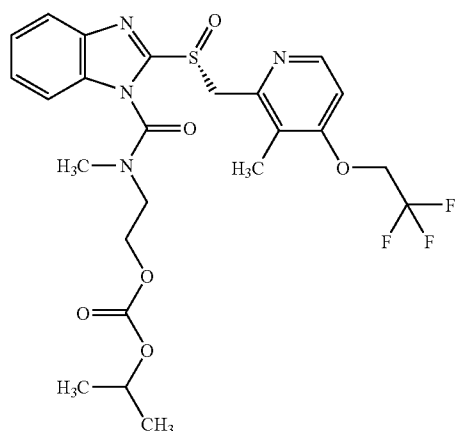
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To a solution (40 mL) of bis(trichloromethyl)carbonate (1.31 g) in tetrahydrofuran was dropwise added a solution (2 mL) of pyridine (1.07 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 10 min., ethyl 2-(methylamino)ethyl carbonate hydrochloride (2.02 g) obtained in Reference Example 14 was added. A solution (2 mL) of triethylamine (1.84 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, water (100 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with 0.2N hydrochloric acid (50 mL) and saturated brine (100 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (50 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (3.69 g), triethylamine (2.09 mL) and 4-dimethylaminopyridine (0.12 g) were added, and the mixture was stirred at 60° C. for 6 hrs. and at room temperature for 8 hrs. After concentration under reduced pressure, water (100 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (100 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=3:7, then ethyl acetate). Crystallization from diethyl ether and recrystallization from diethyl ether gave the title compound (3.84 g) as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.32(3H,t,J=7.2 Hz), 2.23(3H,s), 3.10(3H,bs), 3.50-4.20(2H,br), 4.22(2H,q,J=7.2 Hz), 4.39(2H,q,J=7.9 Hz), 4.45(2H,m), 4.80-5.15(2H,br), 6.65(1H,d,J=5.6 Hz), 7.36-7.50(3H,m), 7.84(1H,d,J=7.8 Hz), 8.35(1H,d,J=5.6 Hz).

## Synthetic Example 15

Isopropyl 2-[methyl[[[R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate



To a solution (30 mL) of bis(trichloromethyl)carbonate (0.50 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., isopropyl 2-(methylamino)ethyl carbonate hydrochloride (0.99 g) obtained in Reference Example 15 was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 1 hr. Bis(trichloromethyl)carbonate (0.50 g), a solution (1

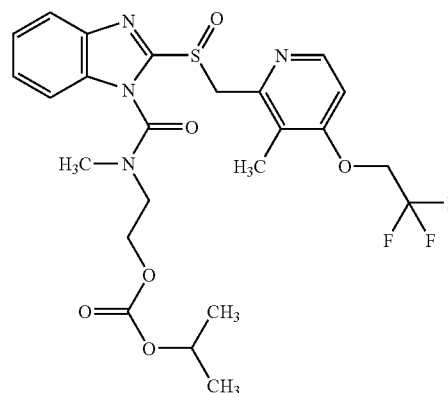
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mL) of pyridine (0.40 mL) in tetrahydrofuran and a solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran were successively added and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.84 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred at 60° C. for 12 hrs. and at room temperature for 3 days. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by flash silica gel column chromatography (eluted with acetone:hexane=1:3, then 3:2), and further by basic silica gel column chromatography (eluted with ethyl acetate:hexane=3:7, then ethyl acetate). Crystallization from diethyl ether and recrystallization from acetone-diisopropyl ether gave the title compound (0.58 g) as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.31(6H,d,J=6.3 Hz), 2.23(3H,s), 3.08(3H,bs), 3.40-4.30(2H,br), 4.37(2H,q,J=7.9 Hz), 4.32-4.53(2H,m), 4.80-5.20(3H,m), 6.63(1H,d,J=5.7 Hz), 7.35-7.50(3H,m), 7.83(1H,d,J=7.2 Hz), 8.34(1H,d,J=5.7 Hz).

## Synthetic Example 16

Isopropyl 2-[methyl[[[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate



To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., isopropyl 2-(methylamino)ethyl carbonate hydrochloride (1.18 g) obtained in Reference Example 15 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was added and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, ethyl acetate (80 mL) and water (30 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (25 mL). 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-py-

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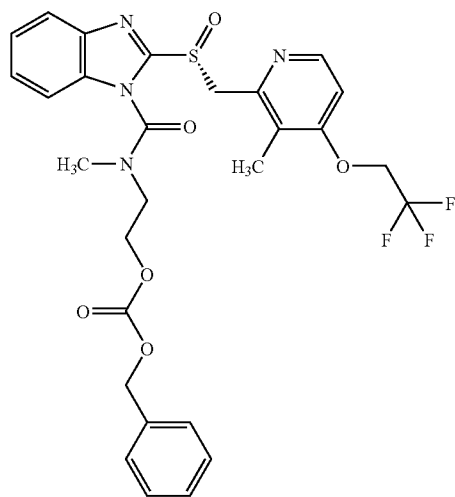
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ridyl)methyl)sulfinyl]-1H-benzimidazole (1.73 g), triethylamine (1.31 mL) and 4-dimethylaminopyridine (0.057 g) were added, and the mixture was stirred at 60° C. for 5 hrs. After concentration under reduced pressure, ethyl acetate (100 mL) and water (50 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate: hexane=1:1), and further by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then 2:1). Crystallization from diisopropyl ether-hexane and recrystallization from diisopropyl ether gave the title compound (1.20 g) as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.31(6H,d,J=6.6 Hz), 2.23(3H,s), 3.08 (3H,bs), 3.50-3.90(2H,bm), 4.38(2H,q,J=7.8 Hz), 4.36-4.58 (2H,bm), 4.79-5.15(3H,m), 6.64(1H,d,J=5.7 Hz), 7.35-7.48 (3H,m), 7.83(1H,d,J=7.5 Hz), 8.34(1H,d,J=5.7 Hz).

## Synthetic Example 17

Benzyl 2-[methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate



To a solution (30 mL) of bis(trichloromethyl)carbonate (0.50 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., benzyl 2-(methylamino)ethyl carbonate hydrochloride (1.08 g) obtained in Reference Example 16 was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred overnight at room temperature. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.84 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred overnight at 60° C. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer

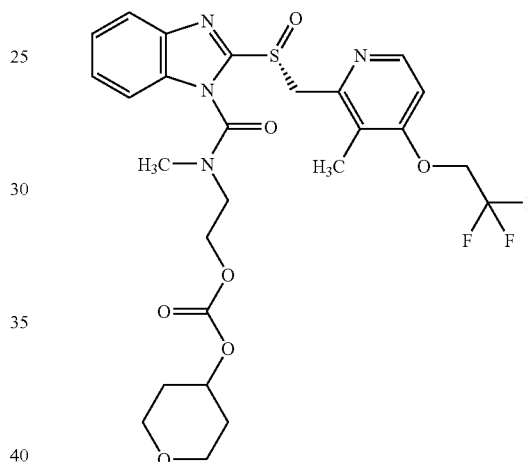
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was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by flash silica gel column chromatography (eluted with acetone:hexane=1:3, then 3:2). Crystallization from acetone-diethyl ether and recrystallization from acetone-diethyl ether gave the title compound (1.17 g) as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.22(3H,s), 3.05(3H,bs), 3.50-4.20 (2H,br), 4.37(2H,q,J=7.8 Hz), 4.46(2H,m), 4.80-5.10(2H,br), 5.17(2H,s), 6.62(1H,d,J=5.6 Hz), 7.26-7.48(8H,m), 7.77-7.88(1H,m), 8.33(1H,d,J=5.6 Hz).

## Synthetic Example 18

2-[Methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl tetrahydropyran-4-yl carbonate



To a solution (20 mL) of bis(trichloromethyl)carbonate (0.48 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.39 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 20 min., 2-(methylamino)ethyl tetrahydropyran-4-yl carbonate hydrochloride (0.96 g) obtained in Reference Example 17 was added. A solution (1 mL) of triethylamine (0.67 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with 0.2N hydrochloric acid (20 mL) and saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.26 g), triethylamine (0.71 mL) and 4-dimethylaminopyridine (0.042 g) were added, and the mixture was stirred at 60° C. for 6 hrs. and at room temperature for 8 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine



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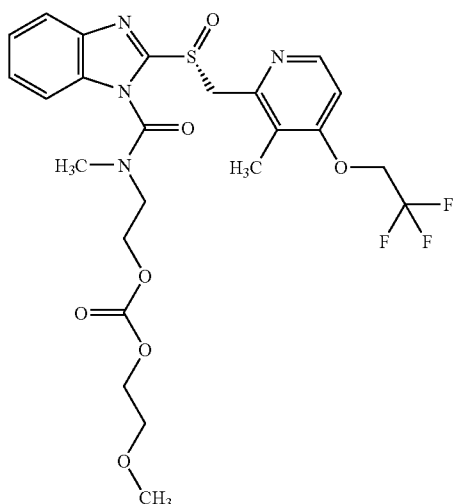
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(50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=3:7, then ethyl acetate). Crystallization from diethyl ether and recrystallization from acetone-diisopropyl ether gave the title compound (1.45 g) as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.64-1.81(2H,m), 1.92-2.03(2H,m), 2.23(3H,s), 3.09(3H,bs), 3.40-4.30(2H,br), 3.45-3.57(2H,m), 3.87-3.97(2H,m), 4.38(2H,q,J=7.8 Hz), 4.45(2H,m), 4.77-5.15(3H,m), 6.64(1H,d,J=5.7 Hz), 7.35-7.50(3H,m), 7.83(1H,d,J=6.9 Hz), 8.35(1H,d,J=5.7 Hz).

## Synthetic Example 19

2-Methoxyethyl 2-[methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate



To a solution (20 mL) of bis(trichloromethyl)carbonate (0.59 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 10 min., 2-methoxyethyl 2-(methylamino)ethyl carbonate hydrochloride (1.07 g) obtained in Reference Example 18 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with 0.2N hydrochloric acid (20 mL) and saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.85 g), triethylamine (1.05 mL) and 4-dimethylaminopyridine (0.061 g) were added, and the mixture was stirred at 60° C. for 6 hrs. and at room temperature for 8 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL)

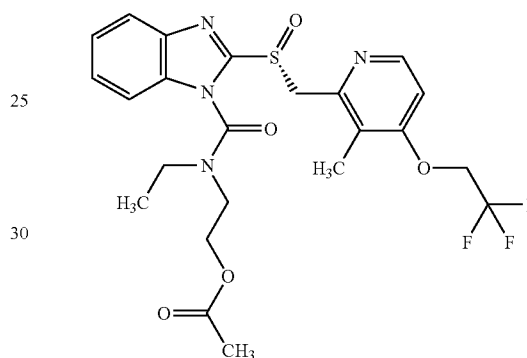
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and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=3:7, then ethyl acetate). Crystallization from ethyl acetate-diethyl ether and recrystallization from ethyl acetate-diisopropyl ether gave the title compound (1.39 g) as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.23(3H,s), 3.09(3H,bs), 3.37(3H,s), 3.50-4.20(2H,br), 3.59-3.65(2H,m), 4.28-4.33(2H,m), 4.38(2H,q,J=7.8 Hz), 4.46(2H,m), 4.80-5.15(2H,br), 6.64(1H,d,J=5.7 Hz), 7.35-7.47(3H,m), 7.83(1H,d,J=7.8 Hz), 8.34(1H,d,J=5.7 Hz).

## Synthetic Example 20

2-[Ethyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate



To a solution (30 mL) of bis(trichloromethyl)carbonate (0.59 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 10 min., 2-(ethylamino)ethyl acetate hydrochloride (0.67 g) obtained in Reference Example 20 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.84 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred overnight at 60° C. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography

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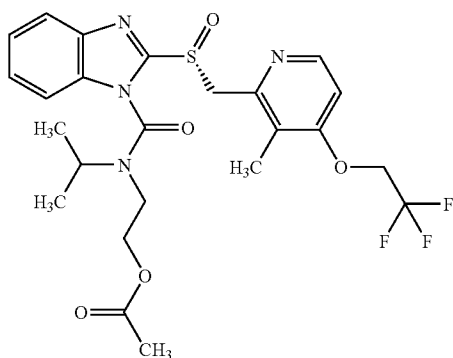
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(eluted with ethyl acetate:hexane=3:7, then ethyl acetate) to give the title compound (1.58 g) as a yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.25(3H,m), 2.08(3H,s), 2.23(3H,s), 3.30-4.10(4H,br), 4.23-4.45(2H,m), 4.38(2H,q,J=7.8 Hz), 4.75-5.20(2H,br), 6.64(1H,d,J=5.7 Hz), 7.35-7.46(3H,m), 7.84(1H,d,J=6.9 Hz), 8.36(1H,d,J=5.7 Hz).

## Synthetic Example 21

2-[Isopropyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate



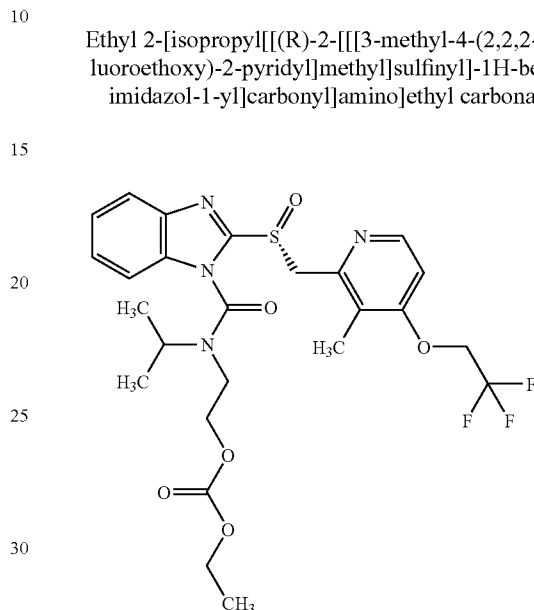
To a solution (10 mL) of bis(trichloromethyl)carbonate (0.543 g) in tetrahydrofuran was dropwise added a solution (5 mL) of pyridine (0.445 mL) in tetrahydrofuran under ice-cooling, and the mixture was stirred at 0° C. for 30 min. 2-(Isopropylamino)ethyl acetate hydrochloride (1.0 g) obtained in Reference Example 22 was added. A solution (5 mL) of triethylamine (0.805 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, water (30 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained oil was dissolved in tetrahydrofuran (5 mL), and added to a solution (20 mL) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.73 g), triethylamine (1.53 mL) and 4-dimethylaminopyridine (0.134 g) in tetrahydrofuran. The mixture was stirred at 40° C. for 12 hrs. The reaction mixture was concentrated under reduced pressure and water (30 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=2:1, then ethyl acetate) to give the title compound (1.50 g) as a pale-yellow amorphous solid.

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<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.20-1.40(6H,m), 2.05(3H×0.4,s), 2.11(3H×0.6,s), 2.18(3H×0.6,s), 2.27(3H×0.4,s), 3.40-3.60(1H,m), 3.70-4.60(6H,m), 4.70-5.25(2H,m), 6.65(1H,d,J=5.8 Hz), 7.30-7.50(3H,m), 7.75-7.90(1H,m), 8.37(1H,d,J=5.8 Hz).

## Synthetic Example 22

Ethyl 2-[isopropyl[[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate



To a solution (10 mL) of bis(trichloromethyl)carbonate (0.467 g) in tetrahydrofuran was dropwise added a solution (5 mL) of pyridine (0.381 mL) in tetrahydrofuran under ice-cooling, and the mixture was stirred at 0° C. for 30 min. Ethyl 2-(isopropylamino)ethyl carbonate hydrochloride (1.0 g) obtained in Reference Example 23 was added to the reaction mixture. A solution (5 mL) of triethylamine (0.69 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at 0° C. for 15 min. and at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure and water (30 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained oil was dissolved in tetrahydrofuran (5 mL), and added to a solution (20 mL) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.48 g), triethylamine (1.32 mL) and 4-dimethylaminopyridine (0.115 g) in tetrahydrofuran, and the mixture was stirred at 40° C. for 12 hrs. The reaction mixture was concentrated under reduced pressure and water (30 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=2:1, then ethyl acetate) to give the title compound (1.20 g) as a pale-yellow amorphous solid.

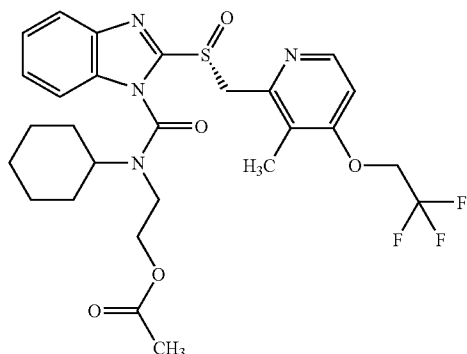
<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.20-1.40(9H,m), 2.17(3H×0.6,s), 2.27(3H×0.4,s), 3.40-3.70(1H,m), 3.75-4.65(8H,m), 4.70-5.30(2H,m), 6.64(1H,d,J=5.8 Hz), 7.35-7.55(3H,m), 7.75-7.90(1H,m), 8.38(1H,d,J=5.8 Hz).

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## Synthetic Example 23

2-[Cyclohexyl][(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate

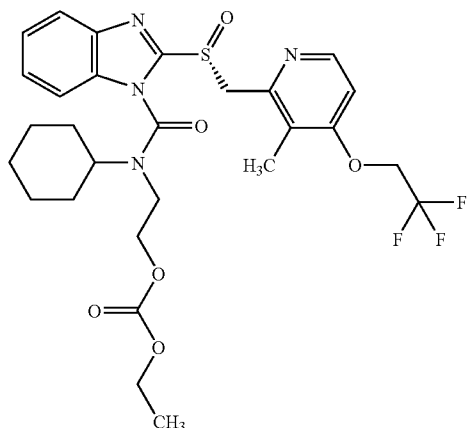


To a solution (10 mL) of bis(trichloromethyl)carbonate (0.593 g) in tetrahydrofuran was dropwise added pyridine (0.485 mL) under ice-cooling. After stirring under ice-cooling for 30 min., 2-(cyclohexylamino)ethyl acetate hydrochloride (1.33 g) obtained in Reference Example 25 was added. Triethylamine (0.84 mL) was dropwise added, and the mixture was stirred at room temperature for 2 hrs. Ethyl acetate (50 mL) was added to the reaction mixture and the mixture was washed with water (50 mL) and saturated brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), and (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.61 g), triethylamine (1.21 mL) and 4-dimethylaminopyridine (0.053 g) were added. The mixture was stirred at 60° C. for 24 hrs. Ethyl acetate (50 mL) was added to the reaction mixture, and the mixture was washed with water (20 mL) and saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (eluted with ethyl acetate:hexane=1:4, then ethyl acetate) to give the title compound (2.12 g) as a pale-yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.00-2.42(16H,m), 3.30-3.70(2H,m), 3.80-4.00(1H,m), 4.27-4.42(2H,m), 4.40(2H,q,J=8.2 Hz), 4.78(1H×0.5,d,J=13.2 Hz), 4.97(2H×0.5,s), 5.20(1H×0.5,d,J=13.2 Hz), 6.67(1H,d,J=5.8 Hz), 7.36-7.46(3H,m), 7.81-7.91(1H,m), 8.39(1H,d,J=5.8 Hz).

## Synthetic Example 24

2-[Cyclohexyl][(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl ethyl carbonate



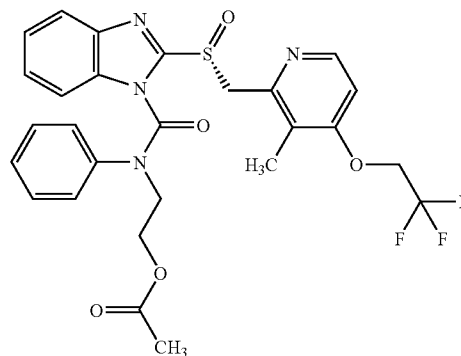
## 102

To a solution (10 mL) of bis(trichloromethyl)carbonate (0.238 g) in tetrahydrofuran was dropwise added pyridine (0.20 mL) under ice-cooling. After stirring under ice-cooling for 30 min., 2-(cyclohexylamino)ethyl ethyl carbonate hydrochloride (0.605 g) obtained in Reference Example 26 was added. Triethylamine (0.335 mL) was dropwise added, and the mixture was stirred at room temperature for 2 hrs. Ethyl acetate (50 mL) was added to the reaction mixture, and the mixture was washed with water (50 mL) and saturated brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (10 mL), and (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (0.60 g), triethylamine (0.45 mL) and 4-dimethylaminopyridine (0.02 g) were added. The mixture was stirred at 60° C. for 24 hrs. Ethyl acetate (50 mL) was added to the reaction mixture, and the mixture was washed with water (20 mL) and saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (eluted with ethyl acetate:hexane=1:4, then ethyl acetate) to give the title compound (0.92 g) as a pale-yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.02-2.27(16H,m), 3.40-4.60(9H,m), 4.78(1H×0.5,d,J=13.2 Hz), 4.97(2H×0.5,s), 5.44(1H×0.5,d,J=13.2 Hz), 6.69(1H,d,J=5.6 Hz), 7.32-7.54(3H,m), 7.80-7.91(1H,m), 8.38(1H,d,J=5.6 Hz).

## Synthetic Example 25

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate



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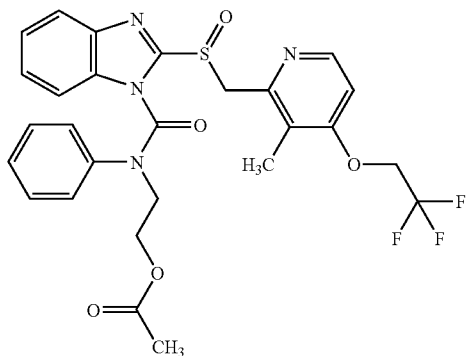
## 103

To a solution (350 mL) of bis(trichloromethyl)carbonate (13.4 g) in tetrahydrofuran was dropwise added pyridine (10.38 mL) under ice-cooling. After stirring under ice-cooling for 30 min., 2-anilinoethyl acetate hydrochloride (25.9 g) obtained in Reference Example 27 was added. Triethylamine (18.4 mL) was dropwise added, and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, ethyl acetate (500 mL) and water (500 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (500 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 2-[(chlorocarbonyl)(phenyl)amino]ethyl acetate. This was dissolved in tetrahydrofuran (300 mL), (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (41.2 g), triethylamine (15.6 mL) and 4-dimethylaminopyridine (1.363 g) were added, and the mixture was stirred at 60° C. for 3 hrs. Ethyl acetate (800 mL) was added to the reaction mixture, and the mixture was washed twice with water (800 mL) and with saturated brine (800 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=3:7, then 1:1). Crystallization from diethyl ether gave the title compound (54.1 g) as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.00(3H,s), 2.25(3H,s), 4.15-4.48(6H,m), 4.83(1H,d,J=13.6 Hz), 5.05(1H,d,J=13.6 Hz), 6.67(1H,d,J=5.4 Hz), 7.03-7.45(8H,m), 7.64-7.69(1H,m), 8.40(1H,d,J=5.4 Hz).

## Synthetic Example 26

2-[[[2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](phenyl)amino]ethyl acetate



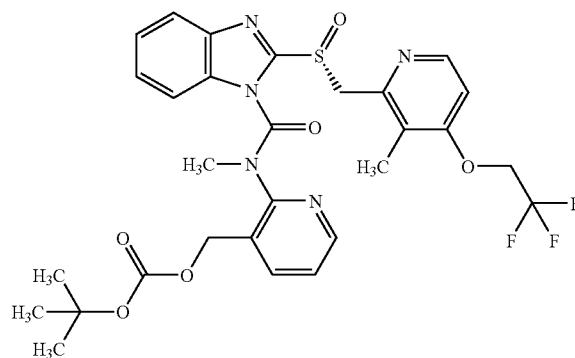
To a solution (10 mL) of 2-[(chlorocarbonyl)(phenyl)amino]ethyl acetate (0.58 g) prepared in the same manner as in Synthetic Example 25 in tetrahydrofuran were added 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (0.739 g), triethylamine (0.558 mL) and 4-dimethylaminopyridine (0.024 g), and the mixture was stirred at 60° C. for 15 hrs. Ethyl acetate (30 mL) was added to the reaction mixture, and the mixture was washed with water (50 mL) and saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (eluted with acetone:hexane=1:4, then 3:2). Crystallization from diethyl ether gave the title compound (0.779 g) as a white solid.

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<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.99(3H,s), 2.25(3H,s), 4.20-4.48(6H,m), 4.83(1H,d,J=13.6 Hz), 5.05(1H,d,J=13.6 Hz), 6.67(1H,d,J=5.8 Hz), 7.03-7.45(8H,m), 7.64-7.69(1H,m), 8.40(1H,d,J=5.8 Hz).

## Synthetic Example 27

tert-Butyl [2-[methyl][(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]-3-pyridyl]methyl carbonate



To a solution (20 mL) of bis(trichloromethyl)carbonate (0.30 g) in tetrahydrofuran was dropwise added pyridine (0.24 mL) under ice-cooling. After stirring under ice-cooling for 30 min., tert-butyl [2-(methylamino)-3-pyridyl]methyl carbonate (0.71 g) obtained in Reference Example 28 was added, and the mixture was stirred at room temperature for 2 hrs. The precipitated solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (0.92 g), triethylamine (0.70 mL) and 4-dimethylaminopyridine (0.031 g) were added, and the mixture was stirred at 60° C. for 1 hr. Water (50 mL) was added to the reaction mixture and the mixture was extracted twice with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (eluted with acetone:hexane=1:2), and further by basic silica gel column chromatography (eluted with ethyl acetate) to give the title compound (0.38 g) as a pale-yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.46(9H,s), 2.25(3H,s), 3.54(3H,s), 4.37(2H,q,J=8.0 Hz), 4.95(2H,s), 5.15(1H,d,J=14.0 Hz), 5.27(1H,d,J=14.0 Hz), 6.63(1H,d,J=5.4 Hz), 7.26-7.45(3H,m), 7.69-7.87(3H,m), 8.33(1H,d,J=5.4 Hz), 8.44-8.46(1H,m).

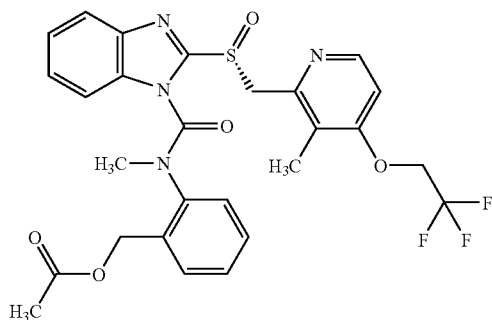


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## Synthetic Example 28

2-[Methyl[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]benzyl acetate

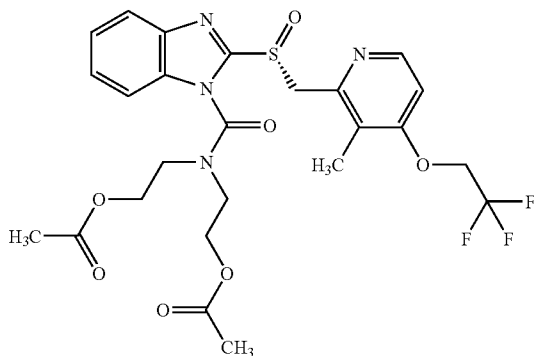


To a solution (30 mL) of bis(trichloromethyl)carbonate (1.46 g) in tetrahydrofuran was dropwise added pyridine (1.16 mL) under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)benzyl acetate (2.57 g) obtained in Reference Example 29 was added. The mixture was stirred at room temperature for 3 hrs. The precipitated solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (40 mL), (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (4.41 g), triethylamine (3.33 mL) and 4-dimethylaminopyridine (0.15 g) were added, and the mixture was stirred at 60° C. for 18 hrs. Water (100 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (eluted with acetone:hexane=1:4, then 1:2). Crystallization from ethyl acetate-diethyl ether-hexane gave the title compound (2.76 g) as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.10(3H,s), 2.00-2.30(3H,br), 3.20-3.50(3H,br), 4.38(2H,q,J=7.6 Hz), 4.70-5.20(2H,m), 5.20-5.50(2H,m), 6.65(1H,d,J=5.4 Hz), 7.10-7.82(8H,m), 8.38(1H,d,J=5.4 Hz).

## Synthetic Example 29

2-[[2-(Acetyloxy)ethyl][[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate



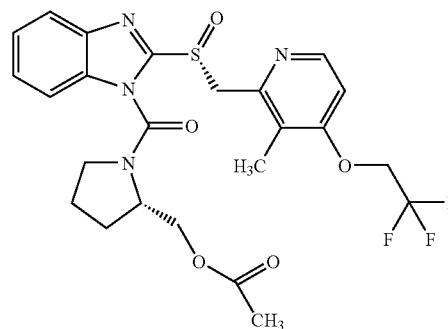
## 106

To a solution (30 mL) of bis(trichloromethyl)carbonate (0.50 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 10 min., 2-[(2-acetyloxyethyl)amino]ethyl acetate hydrochloride (1.13 g) obtained in Reference Example 30 was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2 hrs. The precipitated solid was filtered off and the filtrate was concentrated under reduced pressure. Ethyl acetate (20 mL) was added to the residue, the precipitated solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (30 mL), (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.48 g), triethylamine (1.12 mL) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60° C. overnight. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate), and further by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate). The resulting product was dissolved in ethyl acetate (20 mL), activated carbon was added and the mixture was stirred overnight. The activated carbon was filtered off and the filtrate was concentrated under reduced pressure to give the title compound (1.60 g) as a yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.06(3H,s), 2.08(3H, s), 2.24(3H,s), 3.40-4.45(8H,m), 4.39(2H,q,J=7.9 Hz), 4.88(1H,d,J=13.2 Hz), 5.05(1H,d,J=13.2 Hz), 6.66(1H,d,J=5.6 Hz), 7.38-7.50(3H,m), 7.87(1H,d,J=6.9 Hz), 8.36(1H,d,J=5.6 Hz).

## Synthetic Example 30

[(2S)-1-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]-2-pyrrolidiny]methyl acetate



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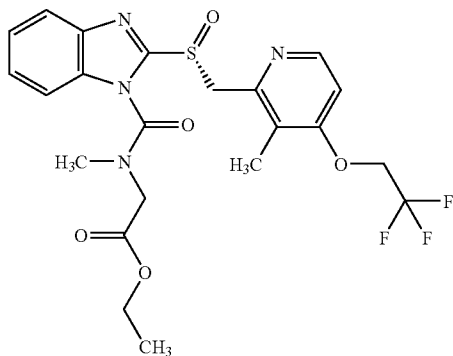
## 107

To a solution (30 mL) of bis(trichloromethyl)carbonate (0.50 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., (S)-2-pyrrolidinylmethyl acetate hydrochloride (0.90 g) obtained in Reference Example 31 was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.84 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred at 60° C. for 1 day and at room temperature for 2 days. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate) and further by silica gel column chromatography (eluted with ethyl acetate:hexane=3:1, then ethyl acetate, then acetone:ethyl acetate=1:4, then 2:3) to give the title compound (0.80 g) as a pale-yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.80-2.30(4H,m), 2.09(3H,s), 2.30(3H,s), 3.39(1H,m), 3.50-3.62(1H,m), 4.20-4.45(4H,m), 4.58(1H,m), 4.89(1H,d,J=13.5 Hz), 4.96(1H,d,J=13.5 Hz), 6.65(1H,d,J=5.9 Hz), 7.36-7.48(3H,m), 7.89(1H,d,J=8.7 Hz), 8.38(1H,d,J=5.9 Hz)

## Synthetic Example 31

Ethyl [methyl]((R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl)carbonyl]amino]acetate



To a solution (30 mL) of bis(trichloromethyl)carbonate (0.50 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., sarcosine ethyl ester hydrochloride (0.77 g) was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 1 hr. The precipitated solid was filtered off and the filtrate was concentrated under reduced pressure. Water (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was

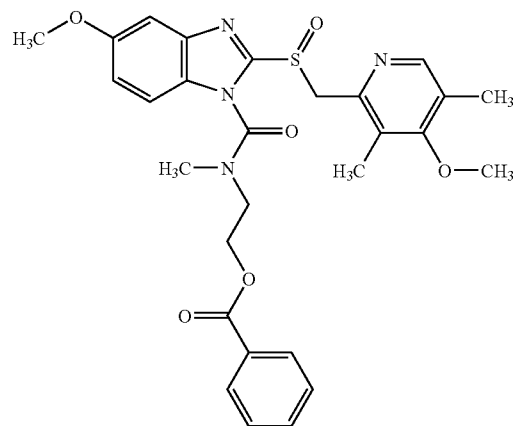
## 108

washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (33 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole sodium (1.37 g) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60° C. overnight. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate) to give the title compound (0.40 g) as a yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.33(3H,t,J=7.1 Hz), 2.24(3H,s), 3.10(3H,bs), 3.70-4.30(2H,br), 4.28(2H,q,J=7.1 Hz), 4.38(2H,q,J=7.8 Hz), 4.82-5.10(2H,br), 6.63(1H,d,J=5.5 Hz), 7.34-7.52(2H,m), 7.70-7.90(2H,m), 8.32(1H,d,J=5.5 Hz).

## Synthetic Example 32

2-[[[5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methylamino)ethyl benzoate



To a solution (10 mL) of bis(trichloromethyl)carbonate (0.344 g) in tetrahydrofuran was dropwise added a solution (5 mL) of pyridine (0.281 mL) in tetrahydrofuran under ice-cooling, and the mixture was stirred at 0° C. for 30 min. 2-(Methylamino)ethyl benzoate hydrochloride (0.750 g) obtained in Reference Example 5 was added. A solution (5 mL) of triethylamine (0.485 mL) in tetrahydrofuran was added, and the mixture was stirred at 0° C. for 1 hr. and at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure and water (30 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained oil was dissolved in tetrahydrofuran (5 mL), added to a solution (10 mL) of 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.0 g), triethylamine (0.808 mL) and 4-dimethylaminopyridine (0.071 g) in tetrahydrofuran, and the mixture was stirred at 40° C. for 18 hrs. The reaction mixture was concentrated under reduced pressure and water (30 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under

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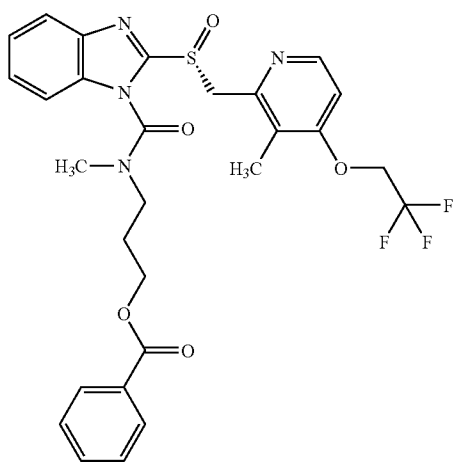
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reduced pressure. The residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate) to give a 1:1 mixture (1.50 g) of the title compound and 2-[[[6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methyl)amino]ethyl benzoate as a pale-yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.05-2.35(6H,m), 3.00-3.30(3H,br), 3.60-4.40(8H,m), 4.60-5.10(4H,m), 6.80-7.00(2H,m), 7.20-7.70(4H,m), 7.95-8.25(3H,m).

## Synthetic Example 33

3-[Methyl][[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]propyl benzoate



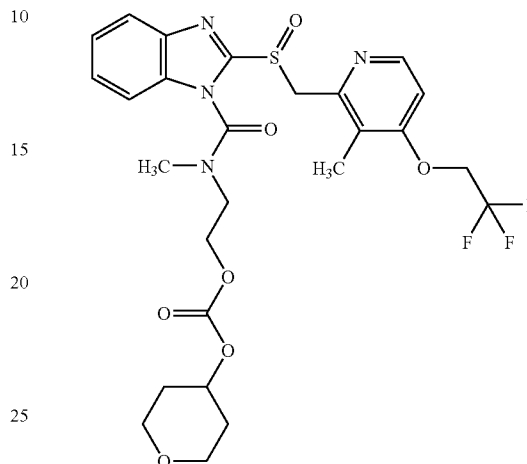
To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.485 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., 3-(methylamino)propyl benzoate hydrochloride (1.38 g) obtained in Reference Example 32 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, water (40 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (25 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (1.63 g), triethylamine (1.23 mL) and 4-dimethylaminopyridine (0.054 g) were added, and the mixture was stirred at 60° C. for 4 hrs. After concentration under reduced pressure, water (40 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (1.26 g) as a yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.21(3H,s), 2.20-2.30(2H,bm), 3.06(3H,bs), 3.60-3.75(2H,bm), 4.36(2H,q,J=7.8 Hz), 4.30-4.50(2H,bm), 4.80-5.15(2H,bm), 6.62(1H,d,J=5.7 Hz), 7.26-7.44(5H,m), 7.54(1H,m), 7.81(1H,m), 7.93-8.03(2H,bm), 8.35(1H,d,J=5.7 Hz).

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## Synthetic Example 34

2-[Methyl][[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl tetrahydropyran-4-yl carbonate



To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.485 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 20 min., 2-(methylamino)ethyl tetrahydropyran-4-yl carbonate hydrochloride (1.43 g) obtained in Reference Example 17 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (20 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL). 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (1.63 g), triethylamine (1.23 mL) and 4-dimethylaminopyridine (0.027 g) were added, and the mixture was stirred at 60° C. for 17.5 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (120 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1), then by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then 2:1). Crystallization from diethyl ether gave the title compound (1.23 g) as a colorless solid.

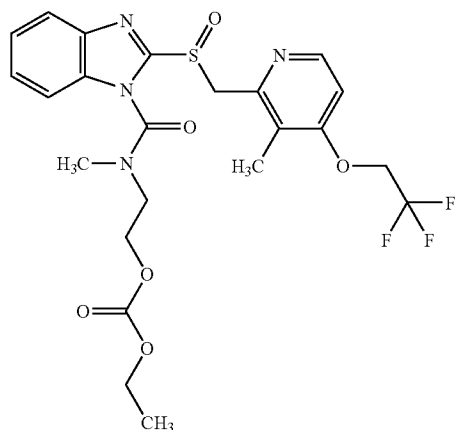
<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.64-1.81(2H,m), 1.92-2.03(2H,m), 2.23(3H,s), 3.10(3H,bs), 3.40-4.30(2H,br), 3.46-3.59(2H,m), 3.87-3.99(2H,m), 4.39(2H,q,J=7.9 Hz), 4.45(2H,m), 4.77-5.15(3H,m), 6.65(1H,d,J=5.4 Hz), 7.35-7.50(3H,m), 7.85(1H,m), 8.36(1H,d,J=5.4 Hz).

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## Synthetic Example 35

Ethyl 2-[methyl[[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate



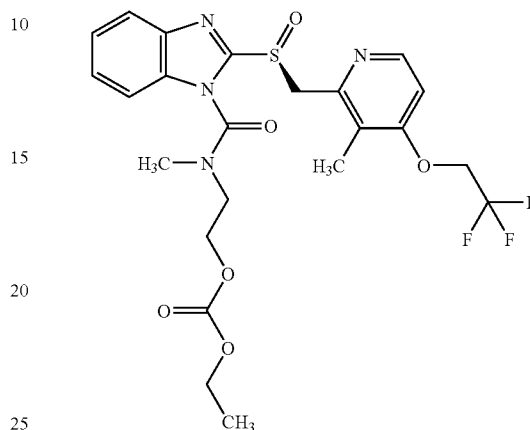
To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.485 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., ethyl 2-(methylamino)ethyl carbonate hydrochloride (1.10 g) obtained in Reference Example 14 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.63 g), triethylamine (1.23 mL), 4-dimethylaminopyridine (0.054 g) was added, and the mixture was stirred at 60° C. for 14 hrs. After concentration under reduced pressure, water (40 µL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (30 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1), and then by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then 2:1) to give the title compound (1.27 g) as a yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.32(3H,t,J=7.1 Hz), 2.23(3H,s), 3.09(3H,bs), 3.50-4.76(4H,br), 4.21(2H,q,J=7.1 Hz), 4.38(2H,q,J=7.9 Hz), 4.84-5.14(2H,m), 6.64(1H,d,J=5.6 Hz), 7.36-7.46(3H,m), 7.83(1H,d,J=7.2 Hz), 8.34(1H,d,J=5.6 Hz).

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## Synthetic Example 36

Ethyl 2-[methyl[(S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate



To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.485 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., ethyl 2-(methylamino)ethyl carbonate hydrochloride (1.10 g) obtained in Reference Example 14 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (30 mL), and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (S)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.15 g), triethylamine (0.87 mL) and 4-dimethylaminopyridine (0.035 g) were added, and the mixture was stirred at 60° C. for 12 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (30 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1). Crystallization from diethyl ether gave the title compound (0.40 g) as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.32(3H,t,J=7.2 Hz), 2.23(3H,s), 3.10(3H,bs), 3.50-4.56(4H,br), 4.22(2H,q,J=7.2 Hz), 4.38(2H,q,J=7.9 Hz), 4.84-5.14(2H,m), 6.65(1H,d,J=5.6 Hz), 7.34-7.50(3H,m), 7.85(1H,m), 8.36(1H,d,J=5.6 Hz).

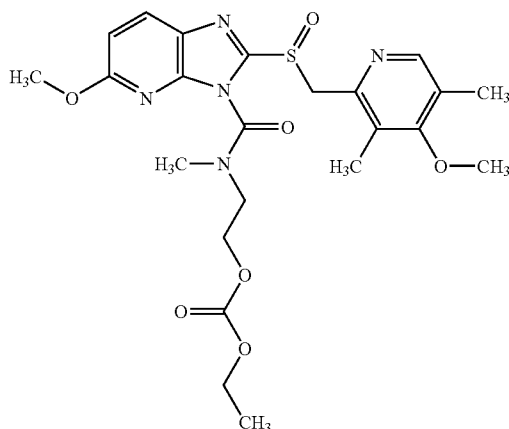


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## Synthetic Example 37

Ethyl 2-[[[5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-yl]carbonyl](methyl)amino]ethyl carbonate



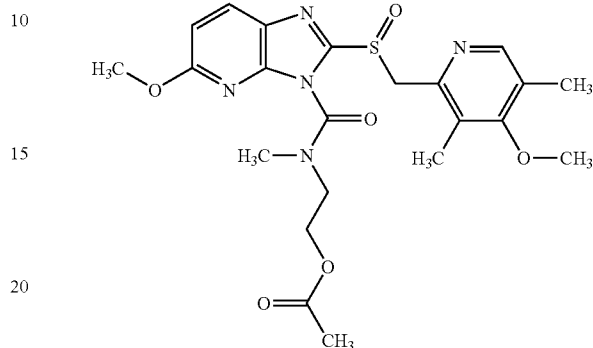
To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.485 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., ethyl 2-(methylamino)ethyl carbonate hydrochloride (1.10 g) obtained in Reference Example 14 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2.5 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). 5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-imidazo[4,5-b]pyridine (1.44 g) synthesized by the method described in JP-A-63-146882, triethylamine (1.16 mL) and 4-dimethylaminopyridine (0.049 g) were added, and the mixture was stirred at 60° C. for 6 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1). Crystallization from diethyl ether gave the title compound (0.721 g) as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.25-1.34(3H,m), 2.23(6H,s), 3.15, 3.32(total 3H,s), 3.72(3H,s), 3.90-4.53(9H,m), 4.86(1H,d, J=13.4 Hz), 4.95(1H,d,J=13.4 Hz), 6.79(1H,d,J=8.7 Hz), 7.95(1H,d,J=8.7 Hz), 8.22(1H,s).

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## Synthetic Example 38

2-[[[5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-yl]carbonyl](methyl)amino]ethyl acetate



To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.485 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl acetate hydrochloride (0.922 g) obtained in Reference Example 2 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (10 mL). 5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-imidazo[4,5-b]pyridine (0.85 g) synthesized by the method described in JP-A-63-146882, triethylamine (0.70 mL) and 4-dimethylaminopyridine (0.025 g) were added, and the mixture was stirred at 60° C. for 5 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue, and the mixture was extracted with ethyl acetate (90 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1). Crystallization from diethyl ether gave the title compound (0.173 g) as a colorless solid.

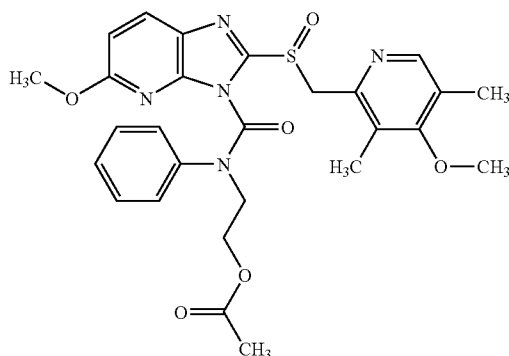
<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.04,2.09(total 3H,s), 2.24(6H,s), 3.13, 3.30(total 3H,s), 3.45-3.97(2H,m), 3.72(3H,s), 3.97(3H,s), 4.15-4.50(2H,m), 4.85(1H,d,J=13.1 Hz), 4.96(1H,d,J=13.1 Hz), 6.80(1H,d,J=8.9 Hz), 7.96(1H,d,J=8.9 Hz), 8.22(1H,s).

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## Synthetic Example 39

2-[[[5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-yl]carbonyl](phenyl)amino]ethyl acetate



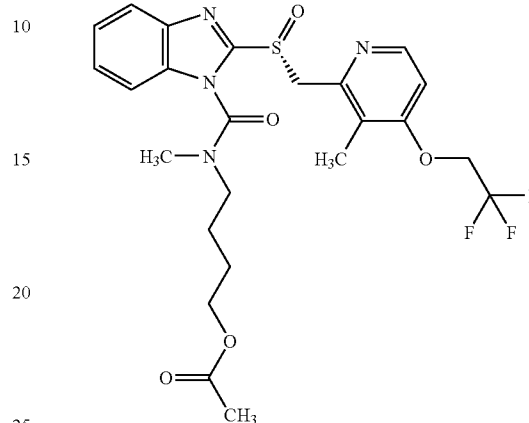
To a solution (10 mL) of bis(trichloromethyl)carbonate (0.291 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.243 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-anilinoethyl acetate hydrochloride (0.647 g) obtained in Reference Example 27 was added. A solution (1 mL) of triethylamine (0.419 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (20 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (10 mL). 5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-imidazo[4,5-b]pyridine (0.867 g) synthesized by the method described in JP-A-63-146882, triethylamine (0.697 mL) and 4-dimethylaminopyridine (0.020 g) was added, and the mixture was stirred at 60° C. for 10 hrs. After concentration under reduced pressure, water (20 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1). Crystallization from diethyl ether gave the title compound (0.311 g) as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.96(3H,s), 2.23(3H,s), 2.25(3H,s), 3.72(3H,s), 4.01(3H,s), 4.12-4.52(4H,m), 4.78-5.22(2H,m), 6.62(1H,d,J=8.7 Hz), 7.02-7.18(3H,m), 7.32-7.48(2H,m), 7.73(1H,d,J=8.7 Hz), 8.26(1H,s).

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## Synthetic Example 40

4-[Methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]butyl acetate



To a solution (20 mL) of bis(trichloromethyl)carbonate (0.59 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 4-(methylamino)butyl acetate hydrochloride (1.08 g) obtained in Reference Example 37 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.02 g), triethylamine (0.77 mL) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60° C. overnight. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (0.93 g) as a yellow amorphous solid.

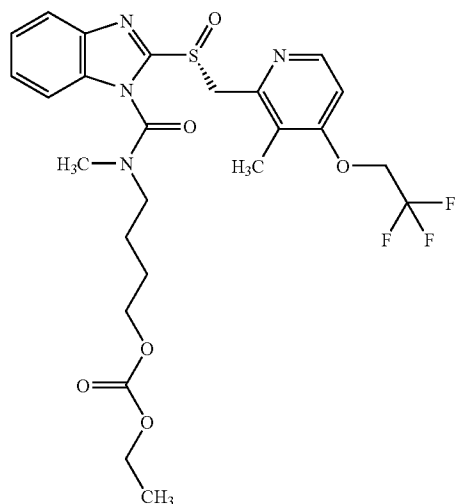
<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.65-1.85(4H,m), 2.03(3H,s), 2.23(3H,s), 3.02(3H,bs), 3.45-3.63(2H,m), 4.03-4.13(2H,m), 4.37(2H,q,J=7.8 Hz), 4.85-5.13(2H,m), 6.64(1H,d,J=5.6 Hz), 7.36-7.46(3H,m), 7.84(1H,d,J=8.4 Hz), 8.35(1H,d,J=5.6 Hz).

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## Synthetic Example 41

Ethyl 4-[methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]butyl carbonate



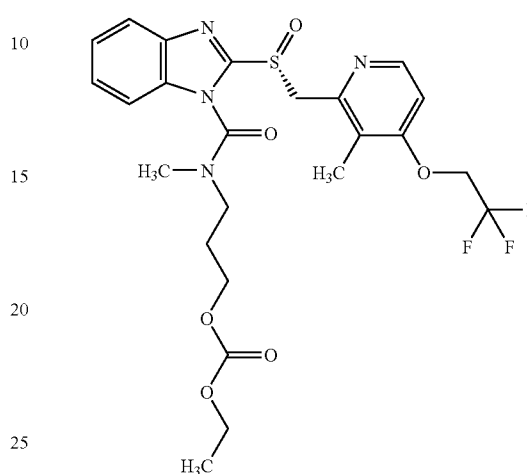
To a solution (20 mL) of bis(trichloromethyl)carbonate (0.59 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., ethyl 4-(methylamino)butyl carbonate hydrochloride (1.27 g) obtained in Reference Example 39 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.26 g), triethylamine (0.95 mL) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60° C. overnight. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate: hexane=1:2, then 1:1) to give the title compound (1.08 g) as a yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.31(3H,t,J=7.2 Hz), 1.73-1.91(4H,m), 2.23(3H,s), 3.01(3H,bs), 3.50-3.62(2H,m), 4.15-4.22(4H,m), 4.38(2H,q,J=7.8 Hz), 4.87-5.13(2H,m), 6.64(1H,d,J=5.4 Hz), 7.35-7.46(3H,m), 7.83(1H,d,J=7.8 Hz), 8.35(1H,d,J=5.4 Hz).

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## Synthetic Example 42

Ethyl 3-[methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]propyl carbonate



To a solution (20 mL) of bis(trichloromethyl)carbonate (0.59 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., ethyl 3-(methylamino)propyl carbonate hydrochloride (1.18 g) obtained in Reference Example 44 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.10 g), triethylamine (0.83 mL) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60° C. overnight. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate: hexane=1:2, then 1:1) to give the title compound (0.88 g) as a yellow amorphous solid.

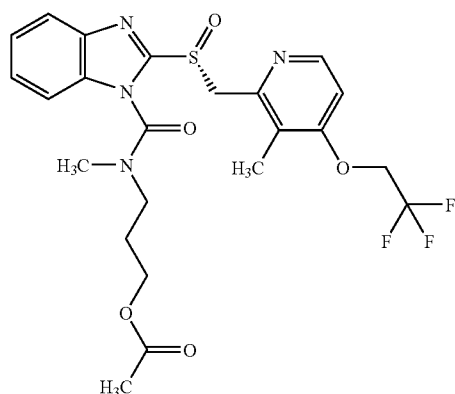
<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.29(3H,t,J=7.2 Hz), 2.10-2.20(2H,m), 2.22(3H,s), 3.02(3H,bs), 3.55-3.77(2H,m), 4.14-4.30(4H,m), 4.37(2H,q,J=7.8 Hz), 4.83-5.13(2H,m), 6.64(1H,d,J=5.6 Hz), 7.35-7.46(3H,m), 7.82(1H,d,J=8.1 Hz), 8.35(1H,d,J=5.6 Hz).

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## Synthetic Example 43

3-[Methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]propyl acetate



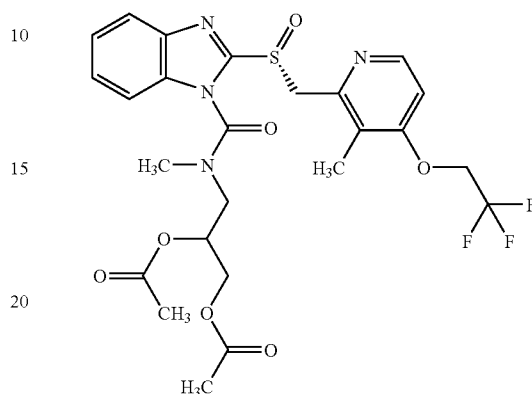
To a solution (40 mL) of bis(trichloromethyl)carbonate (1.19 g) in tetrahydrofuran was dropwise added a solution (2 mL) of pyridine (0.95 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 3-(methylamino)propyl acetate hydrochloride (1.90 g) obtained in Reference Example 42 was added. A solution (2 mL) of triethylamine (1.68 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (100 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (100 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (40 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.99 g), triethylamine (1.50 mL) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60° C. overnight. After concentration under reduced pressure, water (100 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (100 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (1.22 g) as a yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.97(3H,s), 2.05-2.15(2H,m), 2.22(3H,s), 3.03(3H,bs), 3.42-3.72(2H,m), 4.10-4.22(2H,m), 4.37(2H,q,J=7.8 Hz), 4.85-5.13(2H,m), 6.64(1H,d,J=5.6 Hz), 7.24-7.44(3H,m), 7.83(1H,d,J=7.5 Hz), 8.35(1H,d,J=5.6 Hz).

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## Synthetic Example 44

3-[Methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]propane-1,2-diyl diacetate



To a solution (20 mL) of bis(trichloromethyl)carbonate (0.59 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 3-(methylamino)propane-1,2-diyl diacetate hydrochloride (1.35 g) obtained in Reference Example 46 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.27 g), triethylamine (0.96 mL) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60° C. overnight. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (0.64 g) as a yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.05(3H,s), 2.13(3H,s), 2.23(3H,s), 3.07(3H,bs), 3.42-3.95(2H,m), 4.06-4.43(2H,m), 4.38(2H,q,J=7.8 Hz), 4.85-5.05(2H,m), 5.42-5.50(1H,m), 6.63-6.66(1H,m), 7.38-7.51(3H,m), 7.78-7.85(1H,m), 8.33-8.36(1H,m).

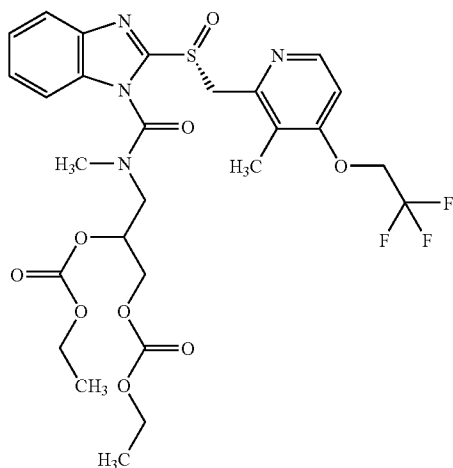


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## Synthetic Example 45

Diethyl 3-[methyl]((R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]propane-1,2-diyl bis-carbonate



To a solution (20 mL) of bis(trichloromethyl)carbonate (0.59 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., diethyl 3-(methylamino)propane-1,2-diyl biscarbonate hydrochloride (1.71 g) obtained in Reference Example 47 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.53 g), triethylamine (1.16 mL) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60° C. overnight. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (1.42 g) as a yellow amorphous solid.

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## Synthetic Example 46

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.28-1.34(6H,m), 2.22(3H,s), 3.07(3H,bs), 3.42-4.60(10H,m), 4.85-5.08(2H,m), 5.30-5.42(1H,m), 6.62-6.64(1H,m), 7.37-7.42(3H,m), 7.80-7.83(1H,m), 8.32-8.35(1H,m).

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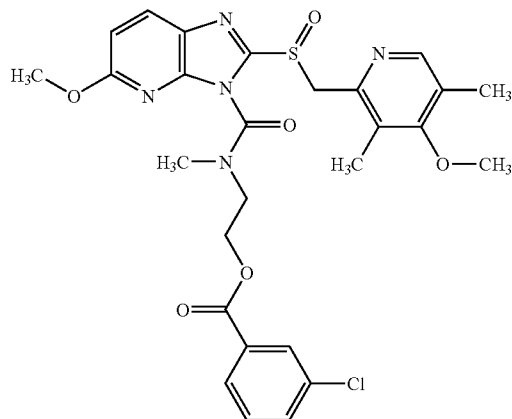
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2-[[[5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl]methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-yl]carbonyl](methyl)amino]ethyl 3-chlorobenzoate



To a solution (7 mL) of bis(trichloromethyl)carbonate (0.194 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.162 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl 3-chlorobenzoate hydrochloride (0.50 g) obtained in Reference Example 7 was added. A solution (1 mL) of triethylamine (0.279 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2.5 hrs. After concentration under reduced pressure, water (15 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (10 mL). 5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl]methyl]sulfinyl]-1H-imidazo[4,5-b]pyridine (0.445 g) synthesized by the method described in JP-A-63-146882, triethylamine (0.357 mL) and 4-dimethylaminopyridine (0.012 g) were added, and the mixture was stirred at 60° C. for 14 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue, and the mixture was extracted with ethyl acetate (70 mL). The ethyl acetate layer was washed with saturated brine (20 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (0.360 g) as a colorless amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.21(3H,s), 2.23(3H,s), 3.32,3.38(total 3H,s), 3.72(3H,s), 3.81(3H,s), 3.92-4.09(2H,m), 4.50-4.73(2H,m), 4.87(1H,d,J=13.4 Hz), 4.94(1H,d,J=13.4 Hz), 6.77

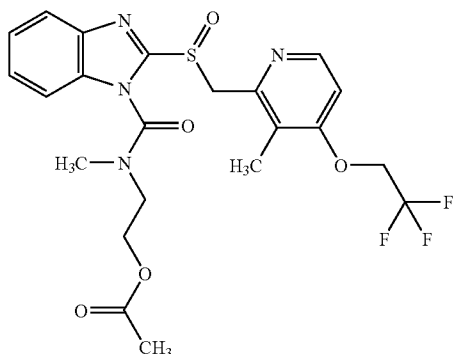
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(1H,d,J=8.8 Hz), 7.36(1H,m), 7.52(1H,m), 7.80-8.03(3H,m), 8.20(1H,s).

## Synthetic Example 47

2-[Methyl[[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate



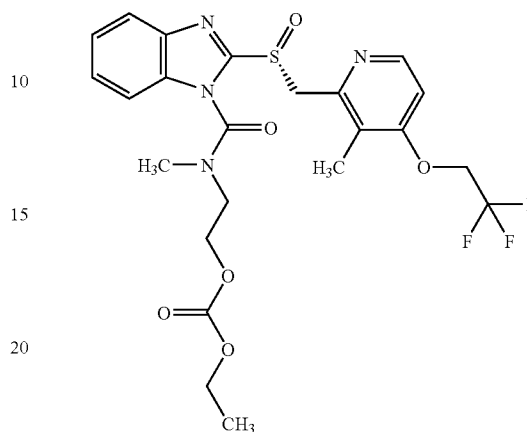
To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.485 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., 2-(methylamino)ethyl acetate hydrochloride (0.922 g) obtained in Reference Example 2 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2.5 hrs. After concentration under reduced pressure, water (40 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (25 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (15 mL). 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.10 g), triethylamine (0.84 mL) and 4-dimethylaminopyridine (0.036 g) were added, and the mixture was stirred at 60° C. for 4.5 hrs. After concentration under reduced pressure, water (40 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then 2:1) to give the title compound (1.18 g) as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.10(3H,s), 2.24(3H,s), 3.09(3H,bs), 3.60-4.00(2H,br), 4.25-4.50(2H,m), 4.38(2H, q,J=7.8 Hz), 4.84-5.18(2H,m), 6.64(1H,d,J=5.6 Hz), 7.36-7.48(3H,m), 7.85(1H,d,J=7.8 Hz), 8.35(1H,d,J=5.6 Hz).

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## Synthetic Example 48

Ethyl 2-[methyl[[[R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate



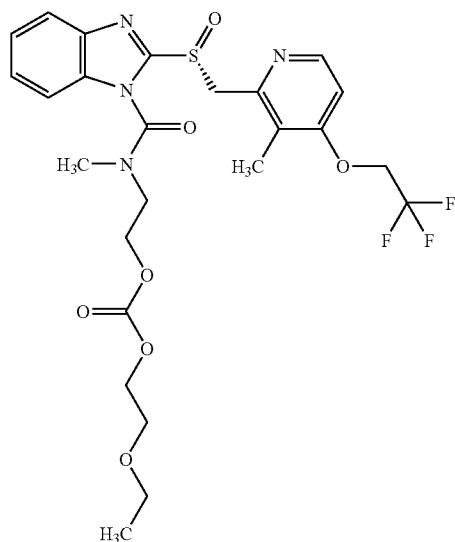
A solution of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (130 g), triethylamine (63.8 mL), 4-dimethylaminopyridine (0.86 g) and 2-[(chlorocarbonyl)(methylamino)ethyl ethyl carbonate (84.8 g) obtained in Reference Example 34 in tetrahydrofuran (813 mL) was stirred at 45-50° C. for 18 hrs. The reaction mixture was concentrated under reduced pressure and water (300 mL) was added to the residue, and the mixture was extracted with ethyl acetate (700 mL). The ethyl acetate layer was washed 3 times with saturated brine (300 mL), and anhydrous magnesium sulfate (130 g) and activated carbon (13 g) were added. The mixture was stirred at room temperature for 30 min. and filtrated. The filtrate was concentrated under reduced pressure and the residue was dissolved in diethyl ether (600 mL) containing triethylamine (0.49 mL), and the mixture was concentrated under reduced pressure. This step was further repeated twice. The obtained oily substance was dissolved in ethanol (200 mL) containing triethylamine (2.45 mL) and water (120 mL) was dropwise added under ice-cooling. The precipitated crystals were collected by filtration, washed 3 times with ice-cooled ethanol-water (volume ratio 1:1, 150 mL) and dried to give the title compound (172.2 g) as a colorless solid. <sup>1</sup>H-NMR(CDCl<sub>3</sub>) showed the same chart as with the compound obtained in Synthetic Example 14.

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## Synthetic Example 49

2-Ethoxyethyl 2-[methyl][(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate



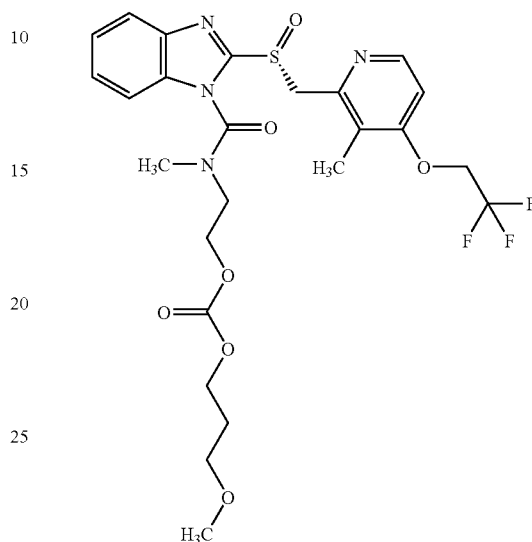
To a solution (20 mL) of bis(trichloromethyl)carbonate (0.43 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.35 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 10 min., 2-ethoxyethyl 2-(methylamino)ethyl carbonate hydrochloride (0.82 g) obtained in Reference Example 48 was added. A solution (1 mL) of triethylamine (0.60 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 days. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with 0.2N hydrochloric acid (20 mL) and saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.63 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred at 60° C. for 6 hrs. and at room temperature for 11 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=3:7, then ethyl acetate:hexane=7:3) to give the title compound (1.39 g) as a yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.19(3H,t,J=6.9 Hz), 2.23(3H,s), 3.09(3H,bs), 3.40-4.20(2H,br), 3.53(2H,q,J=6.9 Hz), 3.63-3.69(2H,m), 4.27-4.34(2H,m), 4.39(2H,q,J=7.8 Hz), 4.47(2H,m), 4.80-5.20(2H,m), 6.65(1H,d,J=5.6 Hz), 7.30-7.52(3H,m), 7.84(1H,d,J=7.5 Hz), 8.35(1H,d,J=5.6 Hz).

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## Synthetic Example 50

3-Methoxypropyl 2-[methyl][(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate



To a solution (20 mL) of bis(trichloromethyl)carbonate (0.53 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.44 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 5 min., 3-methoxypropyl 2-(methylamino)ethyl carbonate hydrochloride (0.82 g) obtained in Reference Example 49 was added. A solution (1 mL) of triethylamine (0.75 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with 0.2N hydrochloric acid (20 mL) and saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.63 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred at 60° C. for 6 hrs. and at room temperature for 6 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=3:7, then ethyl acetate:hexane=7:3). Crystallization from diethyl ether gave the title compound (0.70 g) as a colorless solid.

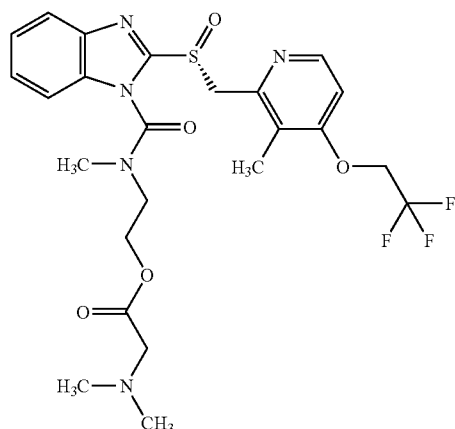
<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.94(2H,quintet,J=6.2 Hz), 2.23(3H,s), 3.09(3H,bs), 3.31(3H,s), 3.40-4.20(2H,br), 3.44(2H,t,J=6.2 Hz), 4.25(2H,t,J=6.5 Hz), 4.38(2H,q,J=7.8 Hz), 4.44(2H,m), 4.80-5.20(2H,m), 6.64(1H,d,J=5.6 Hz), 7.35-7.48(3H,m), 7.83(1H,d,J=7.8 Hz), 8.34(1H,d,J=5.6 Hz).

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## Synthetic Example 51

2-[Methyl[[[*(R)*]-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1*H*-benzimidazol-1-yl]carbonyl]amino]ethyl *N,N*-dimethylglycinate



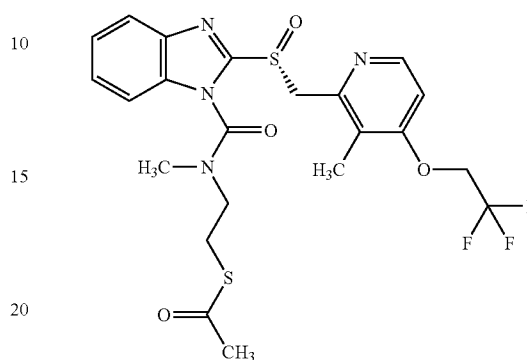
2-(Methylamino)ethyl *N,N*-dimethylglycinate dihydrochloride (1.06 g) obtained in Reference Example 50 was added to tetrahydrofuran (40 mL) and the mixture was stirred for a while, to which bis(trichloromethyl)carbonate (0.77 g) was added. After ice-cooling, a solution (5 mL) of triethylamine (2.17 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 3 hrs. The precipitated solid was filtered off and ethyl acetate (80 mL) was added. The mixture was washed with an ice-cooled aqueous sodium hydrogen carbonate solution (50 mL) and saturated brine (50 mL×2) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (*R*)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1*H*-benzimidazole (1.11 g), triethylamine (0.63 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred at 60° C. for 6 hrs. and at room temperature for 3 days. 4-Dimethylaminopyridine (0.037 g) was added, and the mixture was further stirred at 60° C. for 6 hrs. After concentration under reduced pressure, an aqueous sodium hydrogen carbonate solution (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate, then methanol:ethyl acetate=1:19). Crystallization from diethyl ether gave the title compound (0.41 g) as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.23(3H,s), 2.35(6H,s), 3.08(3H,bs), 3.21(2H,s), 3.50-4.20(2H,br), 4.38(2H,q,J=7.8 Hz), 4.44(2H,m), 4.80-5.18(2H,m), 6.64(1H,d,J=5.6 Hz), 7.36-7.48(3H,m), 7.84(1H,d,J=6.9 Hz), 8.35(1H,d,J=5.6 Hz).

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## Synthetic Example 52

S-[2-[Methyl[[[*(R)*]-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1*H*-benzimidazol-1-yl]carbonyl]amino]ethyl]thioacetate



S-[2-(Methylamino)ethyl]thioacetate hydrochloride (0.75 g) obtained in Reference Example 51 was added to tetrahydrofuran (30 mL) and the mixture was stirred for a while, to which bis(trichloromethyl)carbonate (0.66 g) was added. After ice-cooling, a solution (10 mL) of triethylamine (1.85 mL) in tetrahydrofuran was dropwise added and the mixture was stirred under ice-cooling for 30 min. and at room temperature for 30 min. The precipitated solid was filtered off and ethyl acetate (50 mL) was added to the filtrate. The mixture was washed with ice-cooled 0.2N hydrochloric acid (20 mL) and saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (*R*)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1*H*-benzimidazole (0.96 g), triethylamine (0.54 mL) and 4-dimethylaminopyridine (0.032 g) were added, and the mixture was stirred at 60° C. for 6 hrs. and at room temperature for 8 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with acetone:hexane=3:7, then acetone:hexane=7:3) to give the title compound (1.19 g) as a yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.23(3H,s), 2.34(3H,s), 3.10(3H,bs), 3.22(2H,t,J=6.6 Hz), 3.67(2H,m), 4.38(2H,q,J=7.8 Hz), 4.80-5.20(2H,m), 6.64(1H,d,J=5.7 Hz), 7.35-7.50(3H,m), 7.83(1H,d,J=6.9 Hz), 8.35(1H,d,J=5.7 Hz).

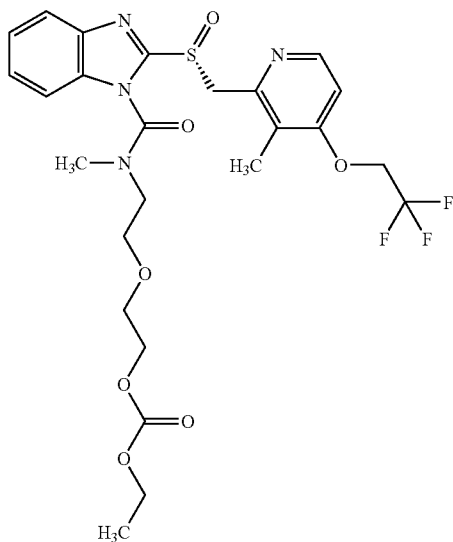


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## Synthetic Example 53

Ethyl 2-[2-[methyl[[*(R)*-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1*H*-benzimidazol-1-yl]carbonyl]amino]ethoxy]ethyl carbonate



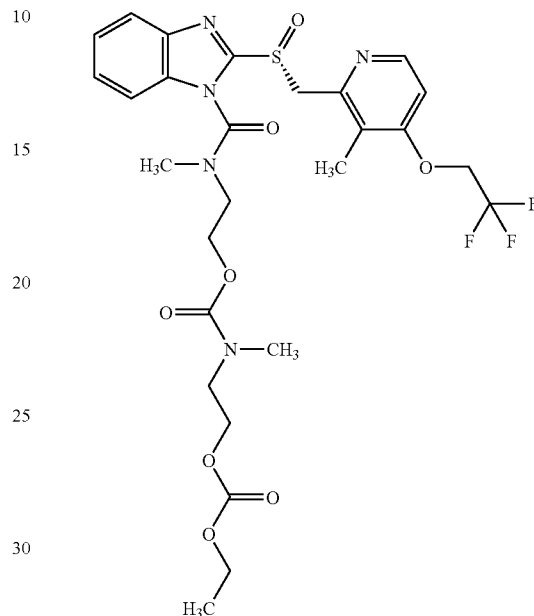
To a solution (40 mL) of bis(trichloromethyl)carbonate (1.19 g) in tetrahydrofuran was dropwise added a solution (2 mL) of pyridine (0.95 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., ethyl 2-[2-(methylamino)ethoxy]ethyl carbonate hydrochloride (2.73 g) obtained in Reference Example 52 was added. A solution (2 mL) of triethylamine (1.68 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (100 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (100 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (40 mL). (*R*)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1*H*-benzimidazole (2.80 g), triethylamine (2.11 mL) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60° C. overnight. After concentration under reduced pressure, water (100 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (100 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (2.19 g) as a yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.28(3H,t,J=7.2 Hz), 2.24(3H,s), 3.10(3H,bs), 3.38-3.80(6H,m), 4.18(2H,q,J=7.2 Hz), 4.27-4.34(2H,m), 4.38(2H,q,J=8.4 Hz), 4.83-5.30(2H,m), 6.65(1H,d,J=5.7 Hz), 7.35-7.50(3H,m), 7.84(1H,d,J=7.8 Hz), 8.36(1H,d,J=5.7 Hz).

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## Synthetic Example 54

Ethyl 2-[methyl[[2-[methyl[[*(R)*-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1*H*-benzimidazol-1-yl]carbonyl]amino]ethoxy]carbonyl]amino]ethyl carbonate



To a solution (20 mL) of bis(trichloromethyl)carbonate (0.59 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., ethyl 2-[methyl[[2-(methylamino)ethoxy]carbonyl]amino]ethyl carbonate hydrochloride (1.71 g) obtained in Reference Example 53 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (*R*)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1*H*-benzimidazole (1.59 g), triethylamine (1.20 mL) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60° C. overnight. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (1.62 g) as a yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.24-1.31(3H,m), 2.24(3H,bs), 2.97-2.99(3H,m), 3.10(3H,bs), 3.55-3.58(2H,m), 4.09-4.50(10H,

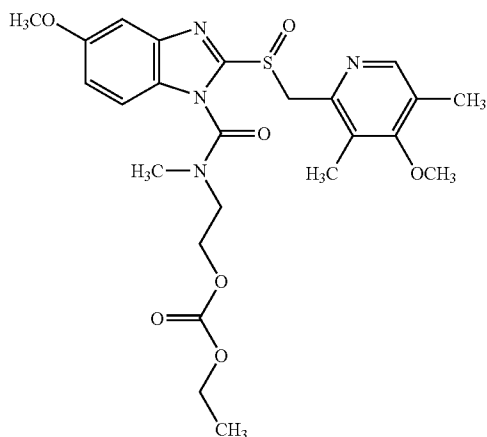
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m), 4.88-5.08(2H,m), 6.65(1H,t,J=5.7 Hz), 7.36-7.48(3H,m), 7.85(1H,d,J=6.9 Hz), 8.36(1H,d,J=5.7 Hz).

## Synthetic Example 55

Ethyl 2-[[[5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methyl)amino]ethyl carbonate



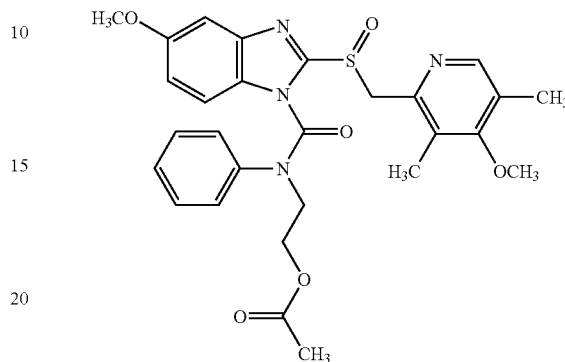
To a solution (10 mL) of bis(trichloromethyl)carbonate (0.291 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.243 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., ethyl 2-(methylamino)ethyl carbonate hydrochloride (0.551 g) obtained in Reference Example 14 was added. A solution (1 mL) of triethylamine (0.418 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, water (15 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (10 mL). 5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (0.817 g), triethylamine (0.661 mL) and 4-dimethylaminopyridine (0.012 g) were added, and the mixture was stirred at 60° C. for 12 hrs. After concentration under reduced pressure, water (20 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give a 3:2 mixture (0.92 g) of the title compound and ethyl 2-[[[6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methyl)amino]ethyl carbonate as a pale-yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.27-1.34(3H,m), 2.10-2.30(3H,m), 2.23(3H,s), 2.99-3.23(3H,m), 3.40-3.85(2H,m), 3.69(6/5H,s), 3.71(9/5H,s), 3.86(6/5H,s), 3.88(9/5H,s), 4.14-4.25(2H,m), 4.38-4.60(2H,m), 4.82-5.06(2H,m), 6.92-7.08(7/5H,m), 7.33(3/5H,d,J=9.0 Hz), 7.66(1H,m), 8.21(1H,s).

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## Synthetic Example 56

2-[[[5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](phenyl)amino]ethyl acetate



To a solution (10 mL) of bis(trichloromethyl)carbonate (0.291 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.243 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-anilinoethyl acetate hydrochloride (0.647 g) obtained in Reference Example 27 was added. A solution (1 mL) of triethylamine (0.419 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (20 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (10 mL). 5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (0.829 g), triethylamine (0.669 mL) and 4-dimethylaminopyridine (0.012 g) were added, and the mixture was stirred at 60° C. for 14 hrs. After concentration under reduced pressure, water (40 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2) to give a 1:1 mixture (1.10 g) of the title compound and 2-[[[6-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](phenyl)amino]ethyl acetate as a colorless amorphous solid.

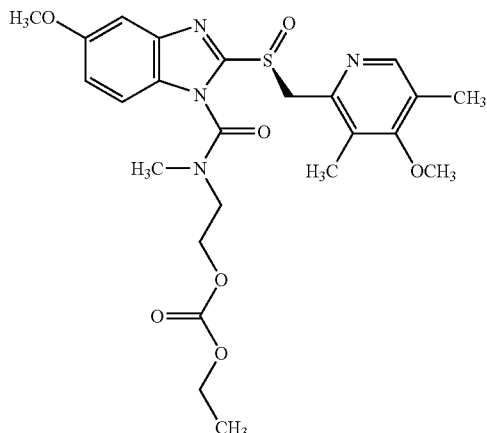
<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.99(3H,s), 2.19(1.5H,s), 2.21(1.5H,s), 2.25(3H,s), 3.70(1.5H,s), 3.71(3H,s), 3.78(1.5H,s), 3.84(1.5H,s), 4.15-4.56(4H,m), 4.74-4.80(1H,m), 4.91-4.98(1H,m), 6.83-6.91(1.5H,m), 7.04-7.19(3.5H,m), 7.25-7.53(2.5H,m), 7.51(0.5H,d,J=8.7 Hz), 8.25(1H,s).

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## Synthetic Example 57

Ethyl 2-[[[(S)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methyl)amino]ethyl carbonate

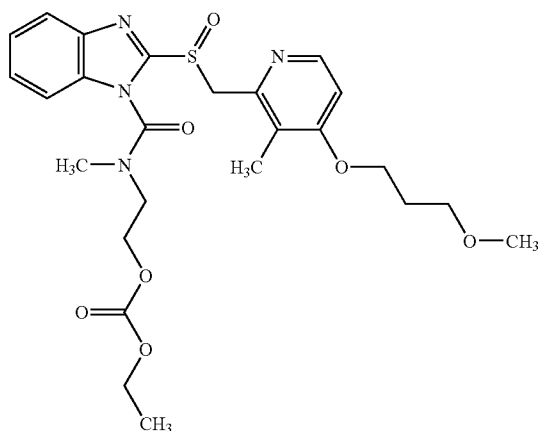


To a solution (10 mL) of (S)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (1.34 g) synthesized by the method described in Synthetic Example 1 of Japanese Patent Application under PCT laid-open under kohyo No. 10-504290 in tetrahydrofuran were added 2-[(chlorocarbonyl)(methyl)amino]ethyl ethyl carbonate (0.9 mL) obtained in Reference Example 34, triethylamine (1.08 mL) and 4-dimethylaminopyridine (0.010 g), and the mixture was stirred at 60° C. for 6 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give a 3:2 mixture (0.92 g) of the title compound and ethyl 2-[[[(S)-6-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methyl)amino]ethyl carbonate as a pale-yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.25-1.34(3H,m), 2.10-2.30(3H,m), 2.23(3H,s), 2.99-3.23(3H,m), 3.40-3.85(2H,m), 3.69(6/5H,s), 3.71(9/5H,s), 3.86(6/5H,s), 3.88(9/5H,s), 4.14-4.25(2H,m), 4.38-4.60(2H,m), 4.79-5.05(2H,m), 6.92-7.08(7/5H,m), 7.33(3/5H,d,J=9.3 Hz), 7.65(1H,m), 8.21(1H,s).

## Synthetic Example 58

Ethyl 2-[[[2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methyl)amino]ethyl carbonate



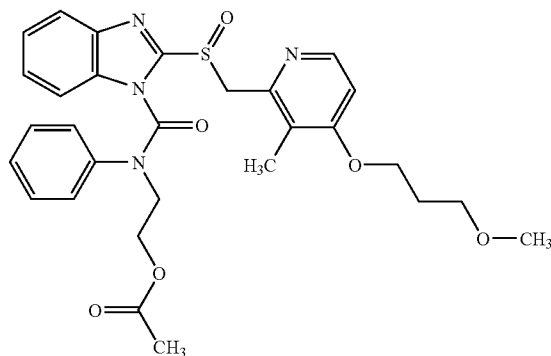
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To a solution (10 mL) of bis(trichloromethyl)carbonate (0.291 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.243 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., ethyl 2-(methylamino)ethyl carbonate hydrochloride (0.551 g) obtained in Reference Example 14 was added. A solution (1 mL) of triethylamine (0.418 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2.5 hrs. After concentration under reduced pressure, water (15 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (10 mL). 2-[[[4-(3-Methoxypropoxy)-3-methyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (0.723 g), triethylamine (0.528 mL) and 4-dimethylaminopyridine (0.012 g) were added, and the mixture was stirred at 60° C. for 17 hrs. After concentration under reduced pressure, water (40 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2), then by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate) to give the title compound (0.44 g) as a colorless amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.31(3H,t,J=7.1 Hz), 2.05(2H,m), 2.18(3H,s), 3.08(3H,bs), 3.34(3H,s), 3.54(2H,t,J=6.1 Hz), 3.61-4.01(2H,m), 4.08(2H,t,J=6.3 Hz), 4.21(2H,t,J=7.1 Hz), 4.38-4.54(2H,m), 4.81-5.12(2H,m), 6.68(1H,d,J=5.6 Hz), 7.34-7.48(3H,m), 7.83(1H,d,J=7.8 Hz), 8.27(1H,d,J=5.6 Hz).

## Synthetic Example 59

2-[[[2-[[[4-(3-Methoxypropoxy)-3-methyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](phenyl)amino]ethyl acetate



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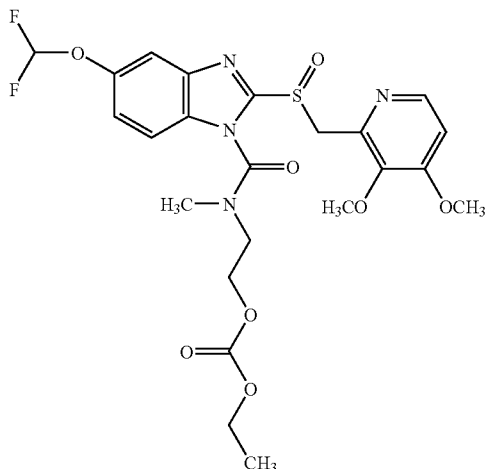
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To a solution (10 mL) of bis(trichloromethyl)carbonate (0.291 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.243 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-anilinoethyl acetate hydrochloride (0.647 g) obtained in Reference Example 27 was added. A solution (1 mL) of triethylamine (0.419 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (20 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (10 mL). 2-[[[4-(3-Methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (0.877 g), triethylamine (0.641 mL) and 4-dimethylaminopyridine (0.012 g) were added, and the mixture was stirred at 60° C. for 16 hrs. After concentration under reduced pressure, water (40 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2), then by silica gel column chromatography (eluted with ethyl acetate) to give the title compound (0.93 g) as a colorless amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.99(3H,s), 2.07(3H,s), 2.19(3H,s), 3.35(3H,s), 3.54(2H,t,J=6.2 Hz), 4.09(2H,t,J=6.2 Hz), 4.14-4.40(4H,m), 4.80(1H,d,J=13.7 Hz), 5.00(1H,d,J=13.7 Hz), 6.71(1H,d,J=5.7 Hz), 7.03-7.34(7H,m), 7.38(1H,m), 7.65(1H,m), 8.32(1H,d,J=5.7 Hz).

## Synthetic Example 60

2-[[[5-(Difluoromethoxy)-2-[[[3,4-dimethoxy-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methyl)amino]ethyl ethyl carbonate



To a solution (8 mL) of bis(trichloromethyl)carbonate (0.174 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.146 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., ethyl 2-(methylamino)ethyl carbonate hydrochloride (0.330 g) obtained in Reference Example 14 was added. A solution (1 mL) of triethylamine (0.250 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (10

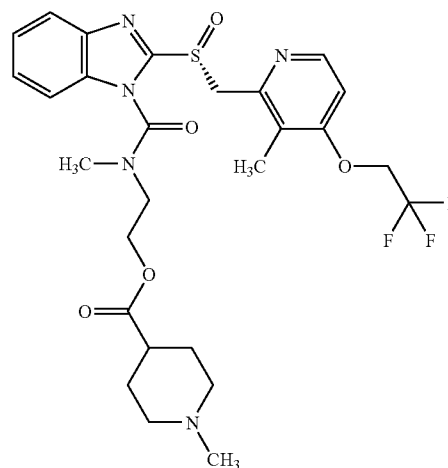
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mL) was added to the residue, and the mixture was extracted with ethyl acetate (30 mL). The ethyl acetate layer was washed with saturated brine (10 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (8 mL). 5-(Difluoromethoxy)-2-[[[3,4-dimethoxy-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (0.432 g), triethylamine (0.279 mL) and 4-dimethylaminopyridine (0.008 g) were added, and the mixture was stirred at 60° C. for 17.5 hrs. After concentration under reduced pressure, water (20 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (10 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1), then by silica gel column chromatography (eluted with ethyl acetate:hexane=2:1, then ethyl acetate) to give a 1:1 mixture (0.09 g) of the title compound and 2-[[[6-(difluoromethoxy)-2-[[[3,4-dimethoxy-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]methylamino]ethyl ethyl carbonate as a pale-yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.31(3H,t,J=7.2 Hz), 3.06(3H,s), 3.42-3.98(2H,m), 3.87(3H,s), 3.90(3H,s), 4.21(2H,q,J=7.2 Hz), 4.36-4.54(2H,m), 4.90(1H,d,J=13.2 Hz), 4.98(1H,d,J=13.2 Hz), 6.54(0.5H,t,J=73.5 Hz), 6.61(0.5H,t,J=73.5 Hz), 6.78(1H,d,J=5.3 Hz), 7.15-7.25(1.5H,m), 7.44(0.5H,d,J=9.0 Hz), 7.59(0.5H,s), 7.80(0.5H,d,J=9.0 Hz), 8.17(1H,d,J=5.3 Hz).

## Synthetic Example 61

2-[Methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl 1-methylpiperidine-4-carboxylate



2-(Methylamino)ethyl 1-methylpiperidine-4-carboxylate dihydrochloride (0.98 g) obtained in Reference Example 54 was added to tetrahydrofuran (50 mL) and the mixture was stirred for a while, to which bis(trichloromethyl)carbonate (0.53 g) was added. After ice-cooling, a solution (50 mL) of triethylamine (2.01 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 3 hrs. Ethyl acetate (100 mL) was added and the mixture was washed with an aqueous sodium hydrogen carbonate solution (100 mL) and saturated brine (80 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahy-



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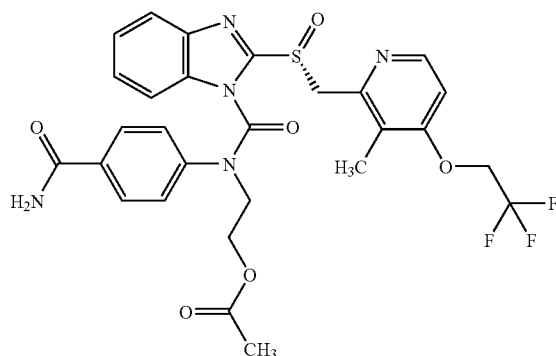
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drofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (0.74 g), triethylamine (0.56 mL) and 4-dimethylaminopyridine (0.049 g) were added, and the mixture was stirred at 60° C. overnight. After concentration under reduced pressure, an aqueous sodium hydrogen carbonate solution (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=7:3, then ethyl acetate, then methanol:ethyl acetate=1:19) to give the title compound (0.78 g) as a yellow-green amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.65-2.05(6H,m), 2.23(3H,s), 2.25(3H,s), 2.24-2.38(1H,m), 2.75-2.85(2H,m), 3.07(3H,bs), 3.40-4.10(2H,br), 4.38(2H,q,J=7.8 Hz), 4.40(2H,m), 4.80-5.10(2H,br), 6.64(1H,d,J=5.6 Hz), 7.36-7.47(3H,m), 7.84(1H,d,J=7.8 Hz), 8.35(1H,d,J=5.6 Hz).

## Synthetic Example 62

2-[[4-(Aminocarbonyl)phenyl]amino]ethyl acetate



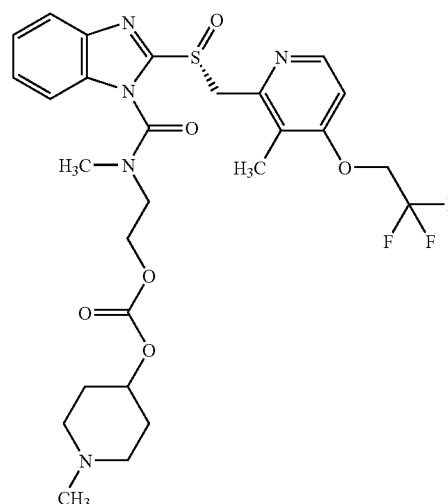
To a solution (20 mL) of bis(trichloromethyl)carbonate (0.45 g) in tetrahydrofuran was dropwise added a solution (10 mL) of 2-[[4-(aminocarbonyl)phenyl]amino]ethyl acetate (0.67 g) obtained in Reference Example 55 and triethylamine (0.63 mL) in tetrahydrofuran under ice-cooling, and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with 0.2N hydrochloric acid (20 mL) and saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (30 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.63 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred at 60° C. for 30 min. and at room temperature overnight. After concentration under reduced pressure, an aqueous sodium hydrogen carbonate solution (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=4:6, then 6:4, then 8:2) to give the title compound (1.26 g) as a yellow amorphous solid.

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<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.99(3H,s), 2.26(3H,s), 4.15-4.55(4H,m), 4.41(2H,q,J=7.9 Hz), 4.80-5.20(2H,br), 6.69(1H,d,J=5.7 Hz), 7.26-7.38(3H,m), 7.48(2H,d,J=8.9 Hz), 7.54(2H,d,J=8.9 Hz), 7.66-7.73(1H,m), 8.39(1H,d,J=5.7 Hz).

## Synthetic Example 63

2-[Methyl[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl 1-methyl-4-piperidiny] carbonate



2-(Methylamino)ethyl 1-methyl-4-piperidiny] carbonate dihydrochloride (1.01 g) obtained in Reference Example 56 was added to tetrahydrofuran (30 mL) and, after stirring for a while, ice-cooled. Bis(trichloromethyl)carbonate (0.69 g) was added and a solution (10 mL) of triethylamine (1.95 mL) in tetrahydrofuran was dropwise added. After stirring under ice-cooling for 1 hr. and at room temperature for 1 hr., the precipitated solid was filtered off. After concentration under reduced pressure, ethyl acetate (50 mL) was added, and the mixture was washed with an ice-cooled aqueous sodium hydrogen carbonate solution (50 mL) and saturated brine (50 mL), and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.63 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred at 60° C. overnight. After concentration under reduced pressure, an aqueous sodium hydrogen carbonate solution (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate, then methanol:ethyl acetate=1:19) to give the title compound (0.70 g) as a yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.70-1.86(2H,m), 1.90-2.04(2H,m), 2.23(3H,s), 2.28(3H,s), 2.10-2.35(2H,m), 2.60-2.72(2H,m), 3.08(3H,bs), 3.40-4.20(2H,br), 4.39(2H,q,J=7.9 Hz),

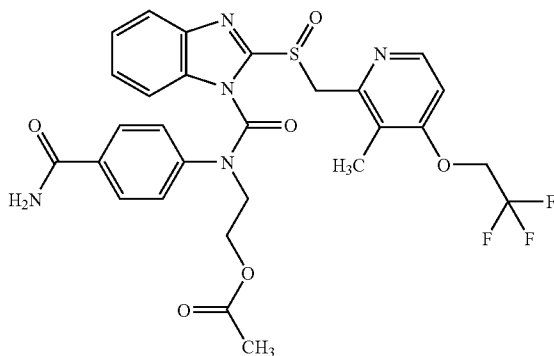
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4.44(2H,m), 4.60-4.74(1H,m), 4.80-5.15(2H,br), 6.65(1H,d, J=5.9 Hz), 7.35-7.52(3H,m), 7.84(1H,d,J=7.5 Hz), 8.35(1H, d,J=5.9 Hz).

## Synthetic Example 64

2-[[4-(Aminocarbonyl)phenyl][[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate



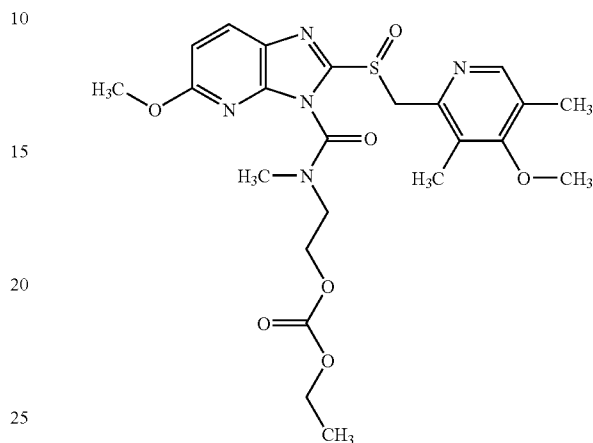
To a solution (5 mL) of bis(trichloromethyl)carbonate (0.12 g) in tetrahydrofuran was dropwise added a solution (5 mL) of 2-[[4-(aminocarbonyl)phenyl]amino]ethyl acetate (0.22 g) obtained in Reference Example 55 and triethylamine (0.17 mL) in tetrahydrofuran under ice-cooling, and the mixture was stirred at room temperature for 30 min. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (30 mL). The ethyl acetate layer was washed with saturated brine (20 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (10 mL). 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (0.37 g), triethylamine (0.28 mL) and 4-dimethylaminopyridine (0.012 g) were added, and the mixture was stirred at 60° C. for 1 hr. After concentration under reduced pressure, an aqueous sodium hydrogen carbonate solution (20 mL) was added to the residue, and the mixture was extracted with ethyl acetate (30 mL). The ethyl acetate layer was washed with saturated brine (20 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=3:7, then 5:5, then 8:2) to give the title compound (0.34 g) as a pale-yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.99(3H,s), 2.26(3H,s), 4.15-4.55(4H,m), 4.41(2H,q,J=7.9 Hz), 4.80-5.20(2H,br), 6.69(1H,d,J=5.9 Hz), 7.26-7.40(3H,m), 7.47(2H,d,J=8.8 Hz), 7.54(2H,d,J=8.8 Hz), 7.65-7.74(1H,m), 8.38(1H,d,J=5.9 Hz).

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## Synthetic Example 65

(-)-Ethyl 2-[[[5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl]methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-yl]carbonyl](methyl)amino]ethyl carbonate



5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl]methyl]sulfinyl]-1H-imidazo[4,5-b]pyridine synthesized according to the method described in JP-A-63-146882 was subjected to preparative HPLC for optical resolution to give a (-) enantiomeric form (0.10 g) thereof. To a solution (5 mL) of this form in tetrahydrofuran were added 2-[(chlorocarbonyl)(methyl)amino]ethyl ethyl carbonate (0.081 g) obtained in Reference Example 34, triethylamine (0.080 mL) and 4-dimethylaminopyridine (0.007 g) and the mixture was stirred at 50° C. for 18 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=2:1) to give the title compound (0.053 g) as a colorless oil.

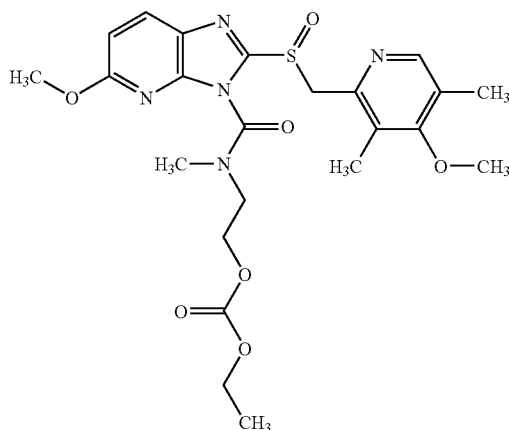
<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.30(3H,t,J=7.1 Hz), 2.24(6H,s), 3.15, 3.32(total 3H,s), 3.73(3H,s), 3.90-4.55(9H,m), 4.85(1H,d,J=13.2 Hz), 4.97(1H,d,J=13.2 Hz), 6.80(1H,d,J=8.8 Hz), 7.96(1H,d,J=8.8 Hz), 8.23(1H,s).

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## Synthetic Example 66

(+)-Ethyl 2-[[[5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-yl]carbonyl](methyl)amino]ethyl carbonate



5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-imidazo[4,5-b]pyridine synthesized according to the method described in JP-A-63-146882 was subjected to preparative HPLC for optical resolution to give a (+) enantiomeric form (0.10 g) thereof. To a solution (5 mL) of this form in tetrahydrofuran were added 2-[(chlorocarbonyl) (methyl)amino]ethyl ethyl carbonate (0.081 g) obtained in Reference Example 34, triethylamine (0.080 mL) and 4-dimethylaminopyridine (0.007 g) and the mixture was stirred at 50° C. for 18 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate: hexane=2:1) to give a 2:1 mixture (0.115 g) of the title compound and (+)-ethyl 2-[[[5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-imidazo[4,5-b]pyridin-1-yl]carbonyl](methyl)amino]ethyl carbonate as a colorless oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.20-1.38(3H,m), 2.24(6H,s), 3.08, 3.15,3.33(total 3H,s), 3.73(3H,s), 3.88-4.55(9H,m), 4.78-5.05(2H,m), 6.80,6.86(1H,d,J=8.8 Hz), 7.76,7.96(1H,d,J=8.8 Hz), 8.21,8.22(total 1H,s).

## Example 1

Among the components described below, 247.7 g of lansoprazole R-isomer (hereinafter, referred to as 'Compound A'), 184.6 g of magnesium carbonate, 492.2 g of purified sucrose, 299.9 g of corn starch and 329.6 g of low substituted hydroxypropyl cellulose were mixed well to obtain a dusting powder. 880 g of sucrose•starch spheres (trade name: Nonpareil-101, produced by Freund Industrial Co., Ltd.) were charged in a centrifugal fluid-bed granulator (CF-360, manufactured by Freund Industrial Co., Ltd.) and the above dusting powder was coated on the sucrose•starch spheres while spraying a hydroxypropyl cellulose solution (2 w/w %), thereby producing spherical granules. The spherical granules were dried at 40° C. for 16 hrs under vacuum and passed through a round sieve to give granules of 710 μm-1400 μm.

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## Composition in 300.0 mg of the granules

5	sucrose•starch spheres	110.0 mg
	Compound A	30.0 mg
	magnesium carbonate	22.4 mg
	purified sucrose	59.8 mg
	corn starch	36.4 mg
10	low substituted hydroxypropyl cellulose	40.0 mg
	hydroxypropyl cellulose	1.4 mg
	total	300.0 mg

## Example 2

25 g of Macrogol 6000 and 10 g of Polysorbate 80 were dissolved in 1206 g of purified water, and 78 g of talc, 25 g of titanium oxide and 866.7 g of methacrylic acid copolymer LD (260 g as solid content) were dispersed into the resulting solution to obtain an enteric coating solution. The granules obtained in Example 1 were coated with the above enteric coating solution using an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltd.) under the condition of inlet air temperature: 45° C., rotor revolution speed: 200 rpm, coating solution spray rate: 3.8 g/min. and spray air pressure: 1.0 kg/cm<sup>2</sup>, followed by drying as it was and passing through a round sieve to give enteric-coated granules of 710 μm-1400 μm having following composition. The obtained spherical granules were dried at 40° C. for 16 hrs under vacuum.

## Composition in 369.2 mg of the enteric-coated granules

35	granules of Example 1	300.0 mg
	methacrylic acid copolymer LD	148.7 mg (44.6 mg as solid content)
	talc	13.8 mg
40	Macrogol 6000	4.4 mg
	titanium oxide	4.4 mg
	Polysorbate 80	2.0 mg
	total	369.2 mg

## Example 3

36 g of methacrylic acid copolymer S, 12 g of methacrylic acid copolymer L and 4.8 g of triethyl citrate were dissolved in a mixed solution of purified water (69.12 g) and absolute ethanol (622.08 g), and 24 g of talc was dispersed into the resulting solution to obtain a coating solution. 100 g of the enteric-coated granules obtained in Example 2 was coated with the above coating solution using an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltd.) under the condition of inlet air temperature: 30° C., rotor revolution speed: 150 rpm, coating solution spray rate: 3.3 g/min. and spray air pressure: 1.0 kg/cm<sup>2</sup> to give controlled release granules having the following composition which is coated with release-controlled coating-layer being soluble pH-dependently (releasing an active ingredient under the circumstances of more than a certain pH value). The resulting spherical granules were passed through a round sieve to give controlled release granules of 710 μm-1400 μm. Then the obtained spherical granules were dried at 40° C. for 16 hrs under vacuum.

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Composition in 605.5 mg of the controlled release granules	
enteric-coated granules of Example 2	369.2 mg
methacrylic acid copolymer S	110.8 mg
methacrylic acid copolymer L	36.9 mg
talc	73.8 mg
triethyl citrate	14.8 mg
total	605.5 mg

## Example 4

24 g of methacrylic acid copolymer S, 24 g of methacrylic acid copolymer L and 4.8 g of triethyl citrate were dissolved in a mixed solution of purified water (69.12 g) and absolute ethanol (622.08 g), and 24 g of talc was dispersed into the resulting solution to obtain coating solution. 100 g of the enteric-coated granules obtained in Example 2 was coated with the above coating solution using an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltd.) under the condition of inlet air temperature: 30° C., rotor revolution speed: 150 rpm, coating solution spray rate: 3.3 g/min. and spray air pressure: 1.0 kg/cm<sup>2</sup> to give controlled release granules having the following composition which is coated with release-controlled coating-layer being soluble pH-dependently (releasing an active ingredient under the circumstances of more than a certain pH value). The resulting spherical granules were passed through a round sieve to give controlled release granules of 710 µm-1400 µm. Then the obtained spherical granules were dried at 40° C. for 16 hrs under vacuum.

Composition in 605.5 mg of the controlled release granules	
enteric-coated granules of Example 2	369.2 mg
methacrylic acid copolymer S	73.85 mg
methacrylic acid copolymer L	73.85 mg
talc	73.8 mg
triethyl citrate	14.8 mg
total	605.5 mg

## Example 5

104 mg of enteric-coated granules obtained in Example 2 and 500 mg of controlled release granules obtained in Example 3 were mixed and thereto 205 mg of polyethylene oxide (trade name: Polyox WSR Coagulant, produced by Dow Chemical Co., Ltd.) was added to obtain a mixture. Two geratin capsules #0 were filled with the resulting mixture to obtain a capsule.

## Example 6

104 mg of enteric-coated granules obtained in Example 2 and 500 mg of controlled release granules obtained in Example 4 were mixed and thereto 205 mg of polyethylene oxide (trade name: Polyox WSR Coagulant, produced by Dow Chemical Co., Ltd.) was added to obtain a mixture. Two geratin capsules #0 were filled with the resulting mixture to obtain a capsule.

## Example 7

300 g of Compound A, 105 g of magnesium carbonate, 195 g of purified sucrose and 75 g of low substituted hydroxypropyl

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cellulose were mixed well to obtain a dusting powder for active ingredient layer. 75 g of purified sucrose, 48.8 g of titanium oxide and 18.8 g of low substituted hydroxypropyl cellulose were mixed well to obtain a dusting powder for intermediate layer. 375 g of sucrose•starch spheres (trade name: Nonpareil-101, produced by Freund Industrial Co., Ltd.) were charged in a centrifugal fluid-bed granulator (CF-360, manufactured by Freund Industrial Co., Ltd.) and the sucrose•starch spheres were coated with the above dusting powder for active ingredient layer while spraying a hydroxypropyl cellulose solution (2 w/w %), thereby producing spherical granules. Then, the resulting spherical granules were coated with the above dusting powder for intermediate layer while spraying a hydroxypropyl cellulose solution (2 w/w %) to obtain spherical granules. The obtained spherical granules were dried at 40° C. for 16 hrs under vacuum and passed through a round sieve to give granules of 710 µm-1400 µm.

Composition in 120.0 mg of the granules	
sucrose•starch spheres	37.5 mg
hydroxypropyl cellulose	0.75 mg
dusting powder for active ingredient layer	
Compound A	30.0 mg
magnesium carbonate	10.5 mg
purified sucrose	19.5 mg
low substituted hydroxypropyl cellulose	7.5 mg
dusting powder for intermediate layer	
purified sucrose	7.5 mg
low substituted hydroxypropyl cellulose	1.875 mg
titanium oxide	4.875 mg
total	120.0 mg

## Example 8

25 g of Macrolog 6000 and 10 g of Polysorbate 80 were dissolved in 1206 g of purified water, and 78 g of talc, 25 g of titanium oxide and 866.7 g of methacrylic acid copolymer LD (260 g as solid content) were dispersed into the resulting solution to obtain an enteric coating solution. The granules obtained in Example 7 were coated with the above enteric coating solution using an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltd.) under the condition of inlet air temperature: 45° C., rotor revolution speed: 200 rpm, coating solution spray rate: 3.8 g/min. and spray air pressure: 1.0 kg/cm<sup>2</sup>, followed by drying as it was and passing through a round sieve to give enteric-coated granules of 710 µm-1400 µm having the following composition. The obtained spherical granules were dried at 40° C. for 16 hrs under vacuum.

Composition in 149.86 mg of the enteric-coated granules	
granules of Example 7	120.00 mg
methacrylic acid copolymer LD	65 mg (19.5 mg as solid content)
talc	5.85 mg
Macrolog 6000	1.88 mg
titanium oxide	1.88 mg
Polysorbate 80	0.75 mg
total	149.86 mg



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## Example 9

36 g of methacrylic acid copolymer S, 12 g of methacrylic acid copolymer L and 4.8 g of triethyl citrate were dissolved in a mixed solution of purified water (69.12 g) and absolute ethanol (622.08 g), and 24 g of talc was dispersed into the resulting solution to obtain a coating solution. 100 g of the enteric-coated granules obtained in Example 8 was coated with the above coating solution using an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltd.) under the condition of inlet air temperature: 30° C., rotor revolution speed: 150 rpm, coating solution spray rate: 3.3 g/min. and spray air pressure: 1.0 kg/cm<sup>2</sup> to give controlled release granules having the following composition which is coated with a release-controlled coating-layer being soluble pH-dependently (releasing an active ingredient under the circumstances of more than a certain pH value). The resulting spherical granules were passed through a round sieve to give controlled release granules of 710 µm-1400 µm. Then the obtained spherical granules were dried at 40° C. for 16 hrs under vacuum.

Composition in 245.86 mg of the controlled release granules	
enteric-coated granules of Example 8	149.86 mg
methacrylic acid copolymer S	45.00 mg
methacrylic acid copolymer L	15.00 mg
talc	30.00 mg
triethyl citrate	6.00 mg
total	245.86 mg

## Example 10

24 g of methacrylic acid copolymer S, 24 g of methacrylic acid copolymer L and 4.8 g of triethyl citrate were dissolved in a mixed solution of purified water (69.12 g) and absolute ethanol (622.08 g), and 24 g of talc was dispersed into the resulting solution to obtain a coating solution. 100 g of the enteric-coated granules obtained in Example 8 was coated with the above coating solution using an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltd.) under the condition of inlet air temperature: 30° C., rotor revolution speed: 150 rpm, coating solution spray rate: 3.3 g/min. and spray air pressure: 1.0 kg/cm<sup>2</sup> to give controlled release granules having the following composition which is coated with a release-controlled coating-layer being soluble pH-dependently (releasing an active ingredient under the circumstances of more than a certain pH value). The resulting spherical granules were passed through a round sieve to give controlled release granules of 710 µm-1400 µm. Then the obtained spherical granules were dried at 40° C. for 16 hrs under vacuum.

Composition in 245.86 mg of the controlled release granules	
enteric-coated granules of Example 8	149.86 mg
methacrylic acid copolymer S	30.0 mg
methacrylic acid copolymer L	30.0 mg
talc	30.0 mg
triethyl citrate	6.0 mg
total	245.86 mg

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## Example 11

35.5 mg of enteric-coated granules obtained in Example 8 and 175 mg of controlled release granules obtained in Example 9 were mixed and thereto 70.2 mg of polyethylene oxide (trade name: Polyox WSR Coagulant, produced by Dow Chemical Co., Ltd.) was added to obtain a mixture. One capsule #1 was filled with the resulting mixture to obtain a capsule (correspond to 30 mg of Compound A).

## Example 12

35.5 mg of enteric-coated granules obtained in Example 8 and 175 mg of controlled release granules obtained in Example 10 were mixed and thereto 70.2 mg of polyethylene oxide (trade name: Polyox WSR Coagulant, produced by Dow Chemical Co., Ltd.) was added to obtain a mixture. One capsule #1 was filled with the resulting mixture to obtain a capsule (correspond to 30 mg of Compound A).

## Experiment Example 1

A capsule obtained in Example 5 was administered orally with 30 ml of water to a fasting beagle dog. Each plasma concentration of Compound A at 1 hr, 2 hrs, 4 hrs, 6 hrs, 7 hrs, 8 hrs and 10 hrs after administration was 186 ng/mL, 132 ng/mL, 107 ng/mL, 303 ng/mL, 355 ng/mL, 216 ng/mL and 113 ng/mL, respectively.

## Experiment Example 2

A capsule obtained in Example 6 was administered orally with 30 ml of water to a fasting beagle dog. Each plasma concentration of Compound A at 1 hr, 2 hrs, 4 hrs, 6 hrs, 7 hrs, 8 hrs and 10 hrs after administration was 192 ng/mL, 137 ng/mL, 473 ng/mL, 478 ng/mL, 364 ng/mL, 257 ng/mL and 28 ng/mL, respectively.

## Experiment Example 3

A capsule obtained in Example 11 was administered orally with 30 ml of water to a fasting beagle dog. Each plasma concentration of Compound A at 1 hr, 2 hrs, 4 hrs, 6 hrs, 7 hrs, 8 hrs and 10 hrs after administration was 308 ng/mL, 245 ng/mL, 323 ng/mL, 81 ng/mL, 39 ng/mL, 26 ng/mL and 0 ng/mL, respectively.

## Experiment Example 4

A capsule obtained in Example 12 was administered orally with 30 ml of water to a fasting beagle dog. Each plasma concentration of Compound A at 1 hr, 2 hrs, 4 hrs, 6 hrs, 7 hrs, 8 hrs and 10 hrs after administration was 160 ng/mL, 319 ng/mL, 631 ng/mL, 371 ng/mL, 230 ng/mL, 144 ng/mL and 25 ng/mL, respectively.

## Example 13

36 g of methacrylic acid copolymer S, 12 g of methacrylic acid copolymer L and 4.8 g of triethyl citrate were dissolved in a mixed solution of purified water (69.12 g) and absolute ethanol (622.08 g), and 24 g of talc was dispersed into the resulting solution to obtain a coating solution. 100 g of the enteric-coated granules obtained in Example 8 was coated with the above coating solution using an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltd.) under the condition of inlet air temperature: 30° C., rotor revolution speed: 150 rpm, coating solution spray rate: 3.3 g/min. and spray air pressure: 1.0 kg/cm<sup>2</sup> to give controlled release granules having the following com-

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position which is coated with a release-controlled coating-layer being soluble pH-dependently (releasing an active ingredient under the circumstances of more than a certain pH value). The resulting spherical granules were passed through a round sieve to give controlled release granules of 710  $\mu\text{m}$ -1400  $\mu\text{m}$ . Then the obtained spherical granules were dried at 40° C. for 16 hrs under vacuum.

Composition in 221.86 mg of the controlled release granules	
enteric-coated granules of Example 8	149.86 mg
methacrylic acid copolymer S	33.75 mg
methacrylic acid copolymer L	11.25 mg
talc	22.5 mg
triethyl citrate	4.5 mg
total	221.86 mg

## Example 14

24 g of methacrylic acid copolymer S, 24 g of methacrylic acid copolymer L and 4.8 g of triethyl citrate were dissolved in a mixed solution of purified water (69.12 g) and absolute ethanol (622.08 g), and 24 g of talc was dispersed into the resulting solution to obtain a coating solution. 100 g of the enteric-coated granules obtained in Example 8 was coated with the above coating solution using an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltd.) under the condition of inlet air temperature: 30° C., rotor revolution speed: 150 rpm, coating solution spray rate: 3.3 g/min. and spray air pressure: 1.0 kg/cm<sup>2</sup> to give controlled release granules having the following composition which is coated with a release-controlled coating-layer being soluble pH-dependently (releasing an active ingredient under the circumstances of more than a certain pH value). The resulting spherical granules were passed through a round sieve to give controlled release granules of 710  $\mu\text{m}$ -1400  $\mu\text{m}$ . Then the obtained spherical granules were dried at 40° C. for 16 hrs under vacuum.

Composition in 221.86 mg of the controlled release granules	
enteric-coated granules of Example 8	149.86 mg
methacrylic acid copolymer S	22.5 mg
methacrylic acid copolymer L	22.5 mg
talc	22.5 mg
triethyl citrate	4.5 mg
total	221.86 mg

## Example 15

35.5 mg of enteric-coated granules obtained in Example 8 and 168 mg of controlled release granules obtained in Example 13 were mixed and thereto 68.2 mg of polyethylene oxide (trade name: Polyox WSR Coagulant, produced by Dow Chemical Co., Ltd.) was added to obtain a mixture. One capsule #1 was filled with the resulting mixture to obtain a capsule (correspond to 30 mg of Compound A).

## Example 16

35.5 mg of enteric-coated granules obtained in Example 8 and 168 mg of controlled release granules obtained in Example 14 were mixed and thereto 68.2 mg of polyethylene oxide (trade name: Polyox WSR Coagulant, produced by

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Dow Chemical Co., Ltd.) was added to obtain a mixture. One capsule #1 was filled with the resulting mixture to obtain a capsule (correspond to 30 mg of Compound A).

## Example 17

35.5 mg of enteric-coated granules obtained in Example 8 and 168 mg of controlled release granules obtained in Example 13 were mixed and the resulting mixture was filled in one capsule #3 to give a capsule (correspond to 30 mg of Compound A).

## Example 18

35.5 mg of enteric-coated granules obtained in Example 8 and 168 mg of controlled release granules obtained in Example 14 were mixed and the resulting mixture was filled in one capsule #3 to give a capsule (correspond to 30 mg of Compound A).

## Experiment Example 5

A capsule obtained in Example 14 was administered orally with 30 ml of water to a fasting beagle dog. Each plasma concentration of Compound A at 1 hr, 2 hrs, 4 hrs, 6 hrs, 7 hrs, 8 hrs and 10 hrs after administration was 403 ng/mL, 687 ng/mL, 803 ng/mL, 463 ng/mL, 329 ng/mL, 217 ng/mL and 65 ng/mL, respectively.

## Example 19

100 g of the granules obtained in Example 1 was charged in a centrifugal fluid-bed granulator (CF-mini, manufactured by Freund Industrial Co., Ltd.) and Ac-Di-Sol that is a disintegrant were coated on the granules by a ratio of 32 w/w % based on the granules while spraying a solution of hydroxypropyl cellulose dissolved in isopropyl alcohol (8 w/w %), thereby producing spherical granules. The spherical granules were dried at 40° C. for 16 hrs under vacuum and passed through a round sieve to give granules of 1400  $\mu\text{m}$  or less.

## Example 20

24 g of aminoalkyl methacrylate copolymer RS was dissolved in acetone (120 g) and isopropyl alcohol (288 g), and 48 g of talc was dispersed into the resulting solution to obtain a coating solution. 100 g of the granules obtained in Example 19 was coated with the above coating solution using an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltd.) under the condition of inlet air temperature: 30° C., rotor revolution speed: 150 rpm, coating solution spray rate: 3.1 g/min. and spray air pressure: 1.0 kg/cm<sup>2</sup> to give controlled release granules having the following composition. The resulting spherical granules were passed through a round sieve to give controlled release granules of 710  $\mu\text{m}$ -1700  $\mu\text{m}$ . Then the obtained spherical granules were dried at 40° C. for 16 hrs under vacuum.

Composition in 130.0 mg of the controlled release granules	
granules of Example 19	100 mg
aminoalkyl methacrylate copolymer RS	10.0 mg
talc	20.0 mg
total	130.0 mg

## Example 21

104 mg of enteric-coated granules obtained in Example 2 and 420 mg of controlled release granules obtained in

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Example 20 were mixed and thereto 175 mg of polyethylene oxide (trade name: Polyox WSR Coagulant, produced by Dow Chemical Co., Ltd.) was added to obtain a mixture. Two gelatin capsules #0 were filled with the resulting mixture to obtain a capsule (correspond to 30 mg of Compound A).

## Example 22

104 mg of enteric-coated granules obtained in Example 2 and 420 mg of controlled release granules obtained in Example 20 were mixed and the resulting mixture was filled in two gelatin capsules #0 to give a capsule (correspond to 30 mg of Compound A).

## Experiment Example 6

A capsule obtained in Example 21 was administered orally with 30 ml of water to a fasting beagle dog. Each plasma concentration of Compound A at 1 hr, 2 hrs, 4 hrs, 6 hrs, 7 hrs, 8 hrs and 10 hrs after administration was 657 ng/mL, 406 ng/mL, 223 ng/mL, 504 ng/mL, 399 ng/mL, 228 ng/mL and 50 ng/mL, respectively.

## Example 23

36 g of methacrylic acid copolymer S, 12 g of methacrylic acid copolymer L and 4.8 g of triethyl citrate were dissolved in a mixed solution of purified water (69.12 g) and absolute ethanol (622.08 g), and 24 g of talc was dispersed into the resulting solution to obtain a coating solution. 100 g of the granules obtained in Example 19 was coated with the above coating solution using an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltd.) under the condition of inlet air temperature: 30° C., rotor revolution speed: 150 rpm, coating solution spray rate: 3.3 g/min. and spray air pressure: 1.0 kg/cm<sup>2</sup> to give controlled release granules having the following composition. The resulting spherical granules were passed through a round sieve to give controlled release granules of 710 µm-1700 µm. Then the obtained spherical granules were dried at 40° C. for 16 hrs under vacuum.

Composition in 164.0 mg of the controlled release granules	
granules of Example 19	100 mg
methacrylic acid copolymer S	30.0 mg
methacrylic acid copolymer L	10.0 mg
talc	20.0 mg
triethyl citrate	4.0 mg
total	164.0 mg

## Example 24

104 mg of enteric-coated granules obtained in Example 2 and 614 mg of controlled release granules obtained in Example 23 were mixed and thereto 239 mg of polyethylene oxide (trade name: Polyox WSR Coagulant, produced by Dow Chemical Co., Ltd.) was added to obtain a mixture. Two gelatin capsules #0 were filled with the resulting mixture to obtain a capsule (correspond to 30 mg of Compound A).

## Example 25

104 mg of enteric-coated granules obtained in Example 2 and 614 mg of controlled release granules obtained in Example 23 were mixed and the resulting mixture was filled in two gelatin capsules #0 to obtain a capsule (correspond to 30 mg of Compound A).

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## Experiment Example 7

A capsule obtained in Example 24 was administered orally with 30 ml of water to a fasting beagle dog. Each plasma concentration of Compound A at 1 hr, 2 hrs, 4 hrs, 6 hrs, 7 hrs, 8 hrs and 10 hrs after administration was 106 ng/mL, 135 ng/mL, 639 ng/mL, 129 ng/mL, 49 ng/mL, 16 ng/mL and 0 ng/mL, respectively.

## Comparison Example 1

One gelatin capsule #0 obtained in Example 2, which was filled with 414 mg of enteric-coated granules, was administered orally with 30 ml of water to a fasting beagle dog. Each plasma concentration of Compound A at 1 hr, 2 hrs, 4 hrs, 6 hrs, 7 hrs, 8 hrs and 10 hrs after administration was 2,068 ng/mL, 689 ng/mL, 70 ng/mL, 0 ng/mL, 0 ng/mL, 0 ng/mL and 0 ng/mL, respectively.

## Example 26

150 g of Compound A, 50 g of magnesium carbonate, 25 g of low substituted hydroxypropyl cellulose and 25 g of hydroxypropyl cellulose were suspended in 1420 g of purified water to obtain a spraying solution. 200 g of crystalline cellulose (sphere) was charged in an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltd.) and was sprayed with the above spraying solution under the condition of inlet air temperature: 62° C., rotor revolution speed: 300 rpm, coating solution spray rate: 10 g/min. and spray air pressure: 1.0 kg/cm<sup>2</sup> to give spherical granules having the following composition. The resulting spherical granules were dried at 40° C. for 16 hrs under vacuum and passed through a round sieve to give controlled release granules of 500 µm-1400 µm.

Composition in 41.24 mg of the granules	
crystalline cellulose (sphere)	22.5 mg
Compound A	11.25 mg
magnesium carbonate	3.75 mg
low substituted hydroxypropyl cellulose	10.0 mg
hydroxypropyl cellulose	1.87 mg
total	41.24 mg

## Example 27

90 g of Compound A, 31.5 g of magnesium carbonate, 58.5 g of purified sucrose and 22.5 g of low substituted hydroxypropyl cellulose were mixed well to obtain a dusting powder of active ingredient layer. 110 g of the granules obtained in Example 26 was charged in a centrifugal fluid-bed granulator (CF-mini, manufactured by Freund Industrial Co., Ltd.) and was coated with the above dusting powder of active ingredient layer while spraying a hydroxypropyl cellulose solution (2 w/w %), thereby producing spherical granules having the following composition. The obtained spherical granules were dried at 40° C. for 16 hrs under vacuum and passed through a round sieve to give granules of 710 µm-1400 µm.

Composition in 118.03 mg of the granules	
granules of Example 26	41.25 mg
Compound A	33.75 mg
magnesium carbonate	11.81 mg

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-continued

Composition in 118.03 mg of the granules	
purified sucrose	21.94 mg
low substituted hydroxypropyl cellulose	8.44 mg
hydroxypropyl cellulose	0.84 mg
total	118.03 mg

## Example 28

The granules obtained in Example 27 were coated with a coating solution for intermediate layer using an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltd.), and were dried intact to give granules having the following composition. The coating solution for intermediate layer was produced by dissolving 20.09 g of hydroxypropyl methylcellulose 2910 in 361.55 g of purified water and followed by dispersing 8.03 g of titanium oxide and 12.05 g of talc into the obtained solution. The coating operation was carried out under the condition of inlet air temperature: 62° C., rotor revolution speed: 200 rpm, coating solution spray rate: 3.0 g/min. and spray air pressure: 1.0 kg/cm<sup>2</sup>. The resulting spherical granules were dried at 40° C. for 16 hrs under vacuum and passed through a round sieve to give granules of 710 µm-1400 µm.

Composition in 133.03 mg of the granules coated with an intermediate layer	
granules of Example 27	118.03 mg
hydroxypropyl methylcellulose 2910	7.5 mg
talc	4.5 mg
titanium oxide	3.0 mg
total	133.03 mg

## Example 29

25 g of Macrogol 6000 and 10 g of Polysorbate 80 were dissolved in 1206 g of purified water, and 78 g of talc, 25 g of titanium oxide and 866.7 g of methacrylic acid copolymer LD (260 g as solid content) were dispersed into the resulting solution to obtain an enteric coating solution. The granules obtained in Example 28 were coated with the above enteric coating solution using an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltd.) under the condition of inlet air temperature: 45° C., rotor revolution speed: 200 rpm, coating solution spray rate: 3.8 g/min. and spray air pressure: 1.0 kg/cm<sup>2</sup>, followed by drying as it was and passing through a round sieve to give enteric-coated granules of 710 µm-1400 µm having the following composition. The obtained spherical granules were dried at 40° C. for 16 hrs under vacuum.

Composition in 165.18 mg of the enteric-coated granules	
granules of Example 28	133.03 mg
methacrylic acid copolymer LD	70 mg (21 mg as solid content)
talc	6.30 mg
Macrogol 6000	2.02 mg

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Composition in 165.18 mg of the enteric-coated granules	
titanium oxide	2.02 mg
Polysorbate 80	0.81 mg
total	165.18 mg

## Example 30

36 g of methacrylic acid copolymer S, 12 g of methacrylic acid copolymer L and 4.8 g of triethyl citrate were dissolved in a mixed solution of purified water (69.12 g) and absolute ethanol (622.08 g), and 24 g of talc was dispersed into the resulting solution to obtain a coating solution. 100 g of the granules obtained in Example 28 was coated with the above coating solution using an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltd.) under the condition of inlet air temperature: 30° C., rotor revolution speed: 100 rpm, coating solution spray rate: 3.0 g/min. and spray air pressure: 1.0 kg/cm<sup>2</sup> to give controlled release granules having the following composition which is coated with a release-controlled coating-layer being soluble pH-dependently (releasing an active ingredient under the circumstances of more than a certain pH value). The resulting spherical granules were passed through a round sieve to give controlled release granules of 1180 µm-1700 µm. Then the obtained spherical granules were dried at 40° C. for 16 hrs under vacuum.

Composition in 196.88 mg of the controlled release granules	
granules of Example 28	133.03 mg
methacrylic acid copolymer S	29.93 mg
methacrylic acid copolymer L	9.98 mg
talc	19.95 mg
triethyl citrate	3.99 mg
total	196.88 mg

## Example 31

24 g of methacrylic acid copolymer S, 24 g of methacrylic acid copolymer L and 4.8 g of triethyl citrate were dissolved in a mixed solution of purified water (69.12 g) and absolute ethanol (622.08 g), and 24 g of talc was dispersed into the resulting solution to obtain a coating solution. 100 g of the granules obtained in Example 28 was coated with the above coating solution using an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltd.) under the condition of inlet air temperature: 30° C., rotor revolution speed: 100 rpm, coating solution spray rate: 3.0 g/min. and spray air pressure: 1.0 kg/cm<sup>2</sup> to give controlled release granules having the following composition which is coated with a release-controlled coating-layer being soluble pH-dependently (releasing an active ingredient under the circumstances of more than a certain pH value). The resulting spherical granules were passed through a round sieve to give controlled release granules of 1180 µm-1700 µm. Then the obtained spherical granules were dried at 40° C. for 16 hrs under vacuum.



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Composition in 196.88 mg of the controlled release granules	
granules of Example 28	133.03 mg
methacrylic acid copolymer S	19.95 mg
methacrylic acid copolymer L	19.95 mg
talc	19.95 mg
triethyl citrate	3.99 mg
total	196.88 mg

## Example 32

28 mg of enteric-coated granules obtained in Example 29 and 98.7 mg of controlled release granules obtained in Example 30 were mixed and thereto 42.3 mg of polyethylene oxide (trade name: Polyox WSR Coagulant, produced by Dow Chemical Co., Ltd.) was added to obtain a mixture. One capsule #1 was filled with the resulting mixture to obtain a capsule (correspond to 30 mg of Compound A).

## Example 33

28 mg of enteric-coated granules obtained in Example 29 and 98.7 mg of controlled release granules obtained in Example 31 were mixed and thereto 42.3 mg of polyethylene oxide (trade name: Polyox WSR Coagulant, produced by Dow Chemical Co., Ltd.) was added to obtain a mixture. One capsule #1 was filled with the resulting mixture to obtain a capsule (correspond to 30 mg of Compound A).

## Example 34

56 mg of enteric-coated granules obtained in Example 29 and 197.4 mg of controlled release granules obtained in Example 30 were mixed and the resulting mixture was filled in one capsule #2 to give a capsule (correspond to 60 mg of Compound A).

## Example 35

84 mg of enteric-coated granules obtained in Example 29 and 296.1 mg of controlled release granules obtained in Example 30 were mixed and the resulting mixture was filled in one capsule #1 to give a capsule (correspond to 90 mg of Compound A).

## Example 36

42 mg of enteric-coated granules obtained in Example 29 and 148.05 mg of controlled release granules obtained in Example 30 were mixed and the resulting mixture was filled in one capsule #3 to give a capsule (correspond to 45 mg of Compound A).

## Example 37

48 g of methacrylic acid copolymer S and 4.8 g of triethyl citrate were dissolved in a mixed solution of purified water (69.12 g) and absolute ethanol (622.08 g), and 24 g of talc was dispersed into the resulting solution to obtain a coating solution. 100 g of the granules obtained in Example 30 was coated with the above coating solution using an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltd.) under the condition of inlet air temperature: 30° C., rotor revolution speed: 100 rpm, coating solution spray rate: 3.0 g/min. and spray air pressure: 1.0 kg/cm<sup>2</sup> to give controlled release granules having the following com-

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position which is coated with a release-controlled coating-layer being soluble pH-dependently (releasing an active ingredient under the circumstances of more than a certain pH value). The resulting spherical granules were passed through a round sieve to give controlled release granules of 1180 μm-1700 μm. Then the obtained spherical granules were dried at 40° C. for 16 hrs under vacuum.

Composition in 207.52 mg of the controlled release granules	
granules of Example 30	196.88 mg
methacrylic acid copolymer S	6.65 mg
talc	3.32 mg
triethyl citrate	0.67 mg
total	207.52 mg

## Example 38

48 g of methacrylic acid copolymer S and 4.8 g of triethyl citrate were dissolved in a mixed solution of purified water (69.12 g) and absolute ethanol (622.08 g), and 24 g of talc was dispersed into the resulting solution to obtain a coating solution. 100 g of the granules obtained in Example 31 was coated with the above coating solution using an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltd.) under the condition of inlet air temperature: 30° C., rotor revolution speed: 100 rpm, coating solution spray rate: 3.0 g/min. and spray air pressure: 1.0 kg/cm<sup>2</sup> to give controlled release granules having the following composition which is coated with a release-controlled coating-layer being soluble pH-dependently (releasing an active ingredient under the circumstances of more than a certain pH value). The resulting spherical granules were passed through a round sieve to give controlled release granules of 1180 μm-1700 μm. Then the obtained spherical granules were dried at 40° C. for 16 hrs under vacuum.

Composition in 207.52 mg of the controlled release granules	
granules of Example 31	196.88 mg
methacrylic acid copolymer S	6.65 mg
talc	3.32 mg
triethyl citrate	0.67 mg
total	207.52 mg

## Example 39

28 mg of enteric-coated granules obtained in Example 29 and 103.8 mg of controlled release granules obtained in Example 37 were mixed and thereto 43.9 mg of polyethylene oxide (trade name: Polyox WSR Coagulant, produced by Dow Chemical Co., Ltd.) was added to obtain a mixture. One capsule #1 was filled with the resulting mixture to obtain a capsule (correspond to 30 mg of Compound A).

## Example 40

28 mg of enteric-coated granules obtained in Example 29 and 103.8 mg of controlled release granules obtained in Example 38 were mixed and thereto 43.9 mg of polyethylene oxide (trade name: Polyox WSR Coagulant, produced by Dow Chemical Co., Ltd.) was added to obtain a mixture. One capsule #1 was filled with the resulting mixture to obtain a capsule (correspond to 30 mg of Compound A).

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## Example 41

56 mg of enteric-coated granules obtained in Example 29 and 207.5 mg of controlled release granules obtained in Example 37 were mixed and the resulting mixture was filled in one capsule #2 to give a capsule (correspond to 60 mg of Compound A).

## Example 42

84 mg of enteric-coated granules obtained in Example 29 and 311.3 mg of controlled release granules obtained in Example 37 were mixed and the resulting mixture was filled in one capsule #1 to give a capsule (correspond to 90 mg of Compound A).

## Example 43

42 mg of enteric-coated granules obtained in Example 29 and 155.6 mg of controlled release granules obtained in Example 37 were mixed and the resulting mixture was filled in one capsule #3 to give a capsule (correspond to 45 mg of Compound A).

## Example 44

300 g of Compound A, 105 g of magnesium carbonate, 195 g of purified sucrose and 75 g of low substituted hydroxypropyl cellulose were mixed well to obtain a dusting powder for active ingredient layer. 75 g of purified sucrose, 48.8 g of titanium oxide and 18.8 g of low substituted hydroxypropyl cellulose were mixed well to obtain a dusting powder for intermediate layer. 375 g of sucrose\*starch spherical granules (trade name: Nonpareil-101, produced by Freund Industrial Co., Ltd.) were charged in a centrifugal fluid-bed granulator (CF-360, manufactured by Freund Industrial Co., Ltd.) and the sucrose\*starch spheres were coated with the above dusting powder for active ingredient layer while spraying a hydroxypropyl cellulose solution (2 w/w %), thereby producing spherical granules. The obtained spherical granules were dried at 40° C. for 16 hrs under vacuum and passed through a round sieve to give granules of 710 µm-1400 µm.

Composition in 158.07 mg of the granules	
sucrose*starch spheres	56.25 mg
hydroxypropyl cellulose	0.57 mg
dusting powder for active ingredient layer	45.00 mg
Compound A	
magnesium carbonate	15.75 mg
purified sucrose	29.25 mg
low substituted hydroxypropylcellulose	11.25 mg
total	158.07 mg

## Example 45

The granules obtained in Example 44 were coated with a coating solution for intermediate layer using an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltd.), and were dried intact to give granules having the following composition. The coating solution for intermediate layer was produced by dissolving 20.09 g of hydroxypropyl methylcellulose 2910 in 361.55 g of purified water and followed by dispersing 8.03 g of titanium oxide and 12.05 g of talc into the obtained solution. The coating operation was carried out under the condition of inlet

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air temperature: 62° C., rotor revolution speed: 200 rpm, coating solution spray rate: 3.0 g/min. and spray air pressure: 1.0 kg/cm<sup>2</sup>. The resulting spherical granules were dried at 40° C. for 16 hrs under vacuum and passed through a round sieve to give granules of 710 µm-1400 µm.

Composition in 188.07 mg of the granules coated with an intermediate layer	
granules of Example 44	158.07 mg
hydroxypropyl methylcellulose 2910	15.00 mg
talc	9.00 mg
titanium oxide	6.00 mg
total	188.07 mg

## Example 46

36 g of methacrylic acid copolymer S, 12 g of methacrylic acid copolymer L and 4.8 g of triethyl citrate were dissolved in a mixed solution of purified water (69.12 g) and absolute ethanol (622.08 g), and 24 g of talc was dispersed into the resulting solution to obtain a coating solution. 100 g of the granules obtained in Example 45 was coated with the above coating solution using an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltd.) under the condition of inlet air temperature: 30° C., rotor revolution speed: 100 rpm, coating solution spray rate: 3.0 g/min. and spray air pressure: 1.0 kg/cm<sup>2</sup> to give controlled release granules having the following composition which is coated with a release-controlled coating-layer being soluble pH-dependently (releasing an active ingredient under the circumstances of more than a certain pH value). The resulting spherical granules were passed through a round sieve to give controlled release granules of 1180 µm-1700 µm. Then the obtained spherical granules were dried at 40° C. for 16 hrs under vacuum.

Composition in 278.35 mg of the controlled release granules	
granules of Example 45	188.07 mg
methacrylic acid copolymer S	42.32 mg
methacrylic acid copolymer L	14.11 mg
talc	28.21 mg
triethyl citrate	5.64 mg
total	278.35 mg

## Example 47

35.5 mg of enteric-coated granules obtained in Example 8 and 139.2 mg of controlled release granules obtained in Example 46 were mixed and thereto 58.2 mg of polyethylene oxide (trade name: Polyox WSR Coagulant, produced by Dow Chemical Co., Ltd.) was added to obtain a mixture. One capsule #1 was filled with the resulting mixture to obtain a capsule (correspond to 30 mg of Compound A).

## Example 48

71 mg of enteric-coated granules obtained in Example 8 and 278.35 mg of controlled release granules obtained in Example 46 were mixed and the resulting mixture was filled in one capsule #1 to give a capsule (correspond to 60 mg of Compound A).

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## Example 49

106.5 mg of enteric-coated granules obtained in Example 8 and 417.5 mg of controlled release granules obtained in Example 46 were mixed and the resulting mixture was filled in two capsules #2 to give a capsule (correspond to 90 mg of Compound A).

## Example 50

53.3 mg of enteric-coated granules obtained in Example 8 and 208.8 mg of controlled release granules obtained in Example 46 were mixed and the resulting mixture was filled in one capsule #2 to give a capsule (correspond to 45 mg of Compound A).

## Example 51

824.4 g of Compound A, 303.2 g of magnesium carbonate, 1062 g of purified sucrose and 228.2 g of low substituted hydroxypropyl cellulose were mixed well to obtain a dusting powder for active ingredient layer. 722.4 g of sucrose\*starch spheres (trade name: Nonpareil-101, produced by Freund Industrial Co., Ltd.) were charged in a centrifugal fluid-bed granulator (CF-360, manufactured by Freund Industrial Co., Ltd.) and the sucrose\*starch spheres were coated with the above dusting powder for active ingredient layer while spraying a hydroxypropyl cellulose solution (2 w/w %), thereby producing spherical granules. The obtained spherical granules were dried at 40° C. for 16 hrs under vacuum and passed through a round sieve to give granules of 710 µm-1400 µm.

Composition in 86.67 mg of the granules	
sucrose*starch spheres	20.64 mg
hydroxypropyl cellulose	0.24 mg
dusting powder for active ingredient layer	22.50 mg
Compound A	
magnesium carbonate	8.25 mg
purified sucrose	28.83 mg
low substituted hydroxypropyl cellulose	6.21 mg
total	86.67 mg

## Example 52

The granules obtained in Example 51 were coated with a coating solution for intermediate layer using a fluid-bed fluidized bed coating machine (MP-10, manufactured by Powrex Co., Ltd.), and were dried intact to give granules having the following composition. The coating solution for intermediate layer was produced by dissolving 270.0 g of hydroxypropyl methylcellulose 2910 in 4874 g of purified water and followed by dispersing 163.5 g of titanium oxide and 108 g of talc into the obtained solution. The coating operation was carried out under the condition of inlet air temperature: 67° C., inlet air volume: 1.5 m<sup>3</sup>/min., coating solution spray rate: 12.0 g/min., spray air pressure: 0.28 MPa and spray air volume: 90 NI/hr. The resulting spherical granules were dried at 40° C. for 16 hrs under vacuum and passed through a round sieve to give granules of 710 µm-1400 µm.

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Composition in 97.50 mg of the granules coated with an intermediate layer	
granules of Example 51	86.67 mg
hydroxypropyl methylcellulose 2910	5.40 mg
talc	2.16 mg
titanium oxide	3.27 mg
total	97.50 mg

## Example 53

57.60 g of Macrogol 6000 and 26.40 g of Polysorbate 80 were dissolved in 2724 g of purified water, and 174 g of talc, 57.6 g of titanium oxide and 19323 g of methacrylic acid copolymer LD (579.6 g as solid content) were dispersed into the resulting solution to obtain an enteric coating solution. The granules obtained in Example 52 were coated with the above enteric coating solution using an agitation fluidized bed granulator (MP-10, manufactured by Powrex Co., Ltd.) under the condition of inlet air temperature: 65° C., inlet air volume: 1.5 m<sup>3</sup>/min., coating solution spray rate: 15.0 g/min. and spray air pressure: 0.30 MPa, and spray air volume: 90 NI/hr. The resulting granules were dried as it was and passed through a round sieve to give enteric-coated granules of 710 µm-1400 µm having the following composition. The obtained spherical granules were dried at 40° C. for 16 hrs under vacuum, and to 1918 g of the granules were added 0.96 g of talc and 0.96 g of aerosil to give enteric-coated granules.

Composition in 120.0 mg of the enteric-coated granules	
granules of Example 52	97.5 mg
methacrylic acid copolymer LD	48.3 mg (14.49 mg as solid content)
talc	4.35 mg
Macrogol 6000	1.44 mg
titanium oxide	1.44 mg
Polysorbate 80	0.66 mg
talc	0.06 mg
aerosil	0.06 mg
total	120.0 mg

## Example 54

1131 g of Compound A, 303.2 g of magnesium carbonate, 750.1 g of purified sucrose and 226.8 g of low substituted hydroxypropyl cellulose were mixed well to obtain a dusting powder for active ingredient layer. 720.0 g of sucrose\*starch spheres (trade name: Nonpareil-101, produced by Freund Industrial Co., Ltd.) were charged in a centrifugal fluid-bed granulator (CF-360, manufactured by Freund Industrial Co., Ltd.) and the sucrose\*starch spheres were coated with the above dusting powder for active ingredient layer while spraying a hydroxypropyl cellulose solution (2 w/w %), thereby producing spherical granules. The obtained spherical granules were dried at 40° C. for 16 hrs under vacuum and passed through a round sieve to give granules of 710 µm-1400 µm.

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Composition in 189.0 mg of the granules	
sucrose•starch spheres	45.0 mg
hydroxypropyl cellulose	0.54 mg
dusting powder for active ingredient layer	67.5 mg
Compound A	
magnesium carbonate	18.0 mg
purified sucrose	44.46 mg
low substituted hydroxypropyl cellulose	13.5 mg
total	189.0 mg

## Example 55

The granules obtained in Example 54 were coated with a coating solution for intermediate layer using a fluid-bed fluidized bed coating machine (MP-10, manufactured by Powrex Co., Ltd.), and were dried intact to give granules having the following composition. The coating solution for intermediate layer was produced by dissolving 236.4 g of hydroxypropyl methylcellulose 2910 in 4255 g of purified water and followed by dispersing 141.6 g of titanium oxide and 94.8 g of talc into the obtained solution. The coating operation was carried out under the condition of inlet air temperature: 65° C., inlet air volume: 1.5 m<sup>3</sup>/min., coating solution spray rate: 12.0 g/min., spray air pressure: 0.26 MPa and spray air volume: 90 NI/hr. The resulting spherical granules were dried at 40° C. for 16 hrs under vacuum and passed through a round sieve to give granules of 710 μm-1400 μm.

Composition in 212.64 mg of the granules coated with an intermediate layer	
granules of Example 54	189.0 mg
hydroxypropyl methylcellulose 2910	11.82 mg
talc	4.74 mg
titanium oxide	7.08 mg
total	212.64 mg

## Example 56

382.8 g of methacrylic acid copolymer S, 127.7 g of methacrylic acid copolymer L and 50.88 g of triethyl citrate were dissolved in a mixed solution of purified water (734.8 g) and absolute ethanol (6614 g), and 255.1 g of talc was dispersed into the resulting solution to obtain a coating solution. The granules obtained in Example 55 was coated with the above coating solution using an agitation fluidized bed granulator (MP-10, manufactured by Powrex Co., Ltd.) under the condition of inlet air temperature: 65° C., inlet air volume: 1.5 m<sup>3</sup>/min., coating solution spray rate: 15.0 g/min., spray air pressure: 0.30 MPa and spray air volume: 90 NI/hr to give controlled release granules having the following composition which is coated with a release-controlled coating-layer being soluble pH-dependently (releasing an active ingredient under the circumstances of more than a certain pH value). The resulting spherical granules were passed through a round sieve to give controlled release granules of 1180 μm-1700 μm. Then the obtained spherical granules were dried at 40° C. for 16 hrs under vacuum, and to 1101 g of the granules were added 0.525 g of talc and 0.525 g of aerosil to give enteric-coated granules.

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Composition in 315.0 mg of the controlled release granules	
granules of Example 55	212.64 mg
methacrylic acid copolymer S	47.85 mg
methacrylic acid copolymer L	15.96 mg
talc	31.89 mg
triethyl citrate	6.36 mg
talc	0.15 mg
aerosil	0.15 mg
total	315.0 mg

## Example 57

120 mg of enteric-coated granules obtained in Example 53 and 315 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #1 to give a capsule (correspond to 90 mg of Compound A).

## Example 58

80 mg of enteric-coated granules obtained in Example 53 and 210 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #2 to give a capsule (correspond to 60 mg of Compound A).

## Example 59

40 mg of enteric-coated granules obtained in Example 53 and 105 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #3 to give a capsule (correspond to 30 mg of Compound A).

## Example 60

240 mg of enteric-coated granules obtained in Example 53 and 210 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #1 to give a capsule (correspond to 90 mg of Compound A).

## Example 61

160 mg of enteric-coated granules obtained in Example 53 and 280 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #1 to give a capsule (correspond to 90 mg of Compound A).

## Example 62

192 mg of enteric-coated granules obtained in Example 53 and 252 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #1 to give a capsule (correspond to 90 mg of Compound A).

## Example 63

160 mg of enteric-coated granules obtained in Example 53 and 210 mg of controlled release granules obtained in



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Example 56 were mixed and the resulting mixture was filled in one capsule #1 to give a capsule (correspond to 75 mg of Compound A).

## Example 64

100 mg of enteric-coated granules obtained in Example 53 and 262.5 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #1 to give a capsule (correspond to 75 mg of Compound A).

## Example 65

133.3 mg of enteric-coated granules obtained in Example 53 and 233.3 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #1 to give a capsule (correspond to 75 mg of Compound A).

## Example 66

200 mg of enteric-coated granules obtained in Example 53 and 175 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #1 to give a capsule (correspond to 75 mg of Compound A).

## Example 67

106.7 mg of enteric-coated granules obtained in Example 53 and 186.7 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #2 to give a capsule (correspond to 60 mg of Compound A).

## Example 68

128 mg of enteric-coated granules obtained in Example 53 and 168 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #2 to give a capsule (correspond to 60 mg of Compound A).

## Example 69

160 mg of enteric-coated granules obtained in Example 53 and 140 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #2 to give a capsule (correspond to 60 mg of Compound A).

## Example 70

60 mg of enteric-coated granules obtained in Example 53 and 157.5 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #2 to give a capsule (correspond to 45 mg of Compound A).

## Example 71

120 mg of enteric-coated granules obtained in Example 53 and 105 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #2 to give a capsule (correspond to 45 mg of Compound A).

## Example 72

80 mg of enteric-coated granules obtained in Example 53 and 140 mg of controlled release granules obtained in

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Example 56 were mixed and the resulting mixture was filled in one capsule #2 to give a capsule (correspond to 45 mg of Compound A).

## Example 73

96 mg of enteric-coated granules obtained in Example 53 and 126 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #2 to give a capsule (correspond to 45 mg of Compound A).

## Example 74

53.3 mg of enteric-coated granules obtained in Example 53 and 93.3 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #3 to give a capsule (correspond to 30 mg of Compound A).

## Example 75

64 mg of enteric-coated granules obtained in Example 53 and 84 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #3 to give a capsule (correspond to 30 mg of Compound A).

## Example 76

80 mg of enteric-coated granules obtained in Example 53 and 70 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #3 to give a capsule (correspond to 30 mg of Compound A).

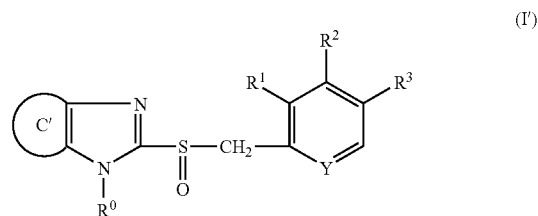
## INDUSTRIAL APPLICABILITY

Since the controlled release preparation of the present invention can extend the therapeutic effective level by controlling the release of active ingredient over a long time, it can provide the effectiveness of treatment with a low dose and the reduction of side effects caused by the rise of blood level, as well as the reduction of administration times.

The invention claimed is:

## 1. A capsule comprising:

composition (i) comprising a tablet, granule or fine granule in which a release of an active ingredient is controlled; said tablet, granule or fine granule comprising a core particle containing an imidazole compound represented by formula (I):



wherein ring C' is an optionally substituted benzene ring or an optionally substituted aromatic monocyclic heterocyclic ring, R<sup>0</sup> is a hydrogen atom, an optionally substituted alkyl group, acyl group or acyloxy group, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are the same or different and are a hydrogen atom, an optionally substituted alkyl group, an optionally substituted alkoxy

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group or an optionally substituted amino group, and Y represents a nitrogen atom or CH; or a salt thereof or an optically active isomer thereof as the active ingredient, and

a pH-dependently soluble release-controlled coating-layer which comprises one kind of polymeric substance or a mixture of two or more kinds of polymeric substances having different release properties selected from the group consisting of hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, carboxymethylethyl cellulose, methyl methacrylate-methacrylic acid copolymer, methacrylic acid-ethyl acrylate copolymer, methacrylic acid-methyl acrylate-methyl methacrylate copolymer, hydroxypropyl cellulose acetate succinate, polyvinyl acetate phthalate and shellac; said polymeric substance is soluble in the pH range of 6.0 to 7.5, and

composition (ii) comprising a tablet, granule or fine granule comprising a core particle containing the active ingredient and enteric coat such that the active ingredient is released in the pH range of no less than 5.0 to no more than 6.0.

2. The capsule according to claim 1, wherein the pH-dependently soluble release-controlled coating-layer is formed on an intermediate layer which is formed on the core particle containing the active ingredient.

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3. The capsule according to claim 1, wherein the active ingredient is lansoprazole.

4. The capsule according to claim 1, wherein the active ingredient is an optically active R-isomer of lansoprazole.

5. The capsule according to claim 1, wherein the active ingredient is an optically active S-isomer of lansoprazole.

6. The capsule according to claim 1, wherein the core particles, which contain the active ingredient and are included in the tablets, granules or fine granules of composition (i) and composition (ii), further contain a basic inorganic salt stabilizer.

7. The capsule according to claim 1, wherein the pH-dependently soluble release-controlled coating-layer of the tablet, granule or fine granule in which the release of the active ingredient is controlled is a layer soluble in the pH range of no less than 6.5 to no more than 7.0.

8. The capsule according to claim 7, wherein the pH-dependently soluble release-controlled coating-layer contains a mixture of two or more kinds of methyl methacrylate-methacrylic acid copolymers having different release properties.

9. The capsule according to claim 1, which further contains a gel-forming polymer.

\* \* \* \* \*